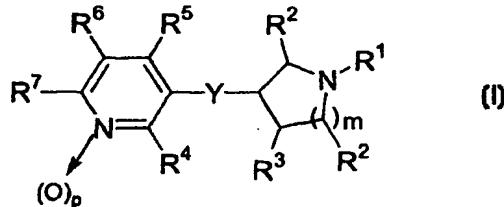


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(54) Title: PYRIDYL ETHERS AND THIOETHERS AS LIGANDS FOR NICOTINIC ACETYLCHOLINE RECEPTOR AND ITS THERAPEUTIC APPLICATION



(57) Abstract

The present invention provides compounds of formula (I) wherein m is 0, 1 or 2; p is 0 or 1; Y is O, S, S(O) or S(O)₂ and R¹ to R⁷ are various substituents as selective modulators of the nicotinic acetylcholine receptor useful in the treatment of pain, Alzheimer's disease, memory loss or dementia or loss of motor function.

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PYRIDYL ETHERS AND THIOETHERS AS LIGANDS FOR NICOTINIC ACETYLCHOLINE RECEPTOR AND ITS THERAPEUTIC APPLICATION

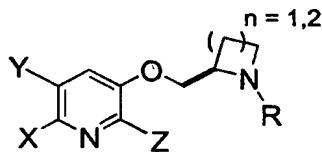
FIELD OF THE INVENTION

Briefly, according to the present invention, there are provided selective modulators of nicotinic acetylcholine receptors. More particularly, the present invention provides pyridyl ethers and thioethers as selective nicotinic acetylcholine receptor agonists, partial agonists, antagonists or allosteric binding molecules useful in the treatment of pain, Alzheimer's disease, memory loss or dementia or loss of motor function.

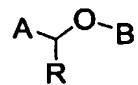
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BACKGROUND OF THE INVENTION

Holladay, et. al., in "Identification and Initial Structure-Activity Relationship of (R)-5-(2-Azetidinylmethoxy)-2-chloropyridine (ABT594), a Potent, Orally Active, Non-Opiate Analgesic Agent Acting via Neuronal Nicotinic Acetylcholine Receptors" , 1998, J. Med. Chem., 41, 407, describe the preparation of ABT594 and its therapeutic utility. A similar disclosure is made by Donnelly-Roberts, et. al., 1998, J. Pharmacol. Exp. Ther., 285, 777 & 787; Decker, et. al., 1998, Eur. J. Pharmacol., 346, 23 and in WO 98/25920; wherein ABT594 is contained within the general structure:

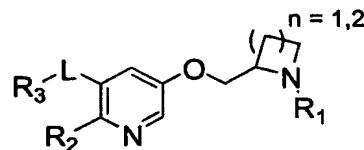


20 *Abreo, et. al.*, in "Heterocyclic Ether Compounds that enhance Cognitive Function", 1994, W.O. Patent 94/08992, describes the preparation of heterocyclic ether compounds and its therapeutic utility. A similar disclosure is made in *Abreo, et. al.*, 1996, *J. Med. Chem.* 39, 817. Generally, the heterocyclic ether compounds have the structure:



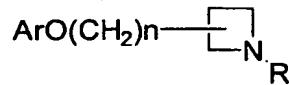
where A is saturated heterocycle, B is unsaturated heterocycle and R is H or C₁₋₆alkyl.

5 *Lin, et. al.*, in "3-Pyridyloxymethyl Heterocyclic ether Compounds useful
in Controlling Chemical Synaptic Transmission", 1997, U.S. Patent 5,629,325,
describe the preparation of pyridyl ether compound and its therapeutic utility.
A similar disclosure is made by *Lin, et. al.*, 1997, *J. Med. Chem.* 40, 385.
Generally, the 3-Pyridyloxymethyl heterocyclic ether compounds have the
10 structure:



wherein R₁ is H or C₁₋₆alkyl; R₂ is H, F, Cl, vinyl or phenyl; L is a C₁₋₆ linking group and R₃ is H or C₁₋₆alkyl.

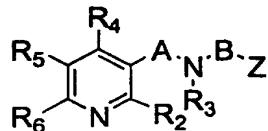
15 *Shanklin, et. al.*, in "Aryloxy and Aryloxyalklazetidines as Antiarrhythmic and Anticonvulsant Agents", 1992, U.S. Patent 5,130,309, describe the preparation of Aryloxy and aryloxyalkylazetidines and their therapeutic utilities. Generally, the described azetidines have the formula:



20 wherein n is 0 to 3, R is H, C₁₋₄alkyl or arylalkyl and Ar is phenyl or substituted phenyl.

Cosford, et. al., in "Substituted Pyridine Derivatives, Their Preparation and Their Use as Modulators of Acetylcholine Receptors", 1996, W.O. Patent 96/31475, describe the preparation of substituted pyridine derivatives and its therapeutic utility. Generally, the pyridine derivative have the formula:

5

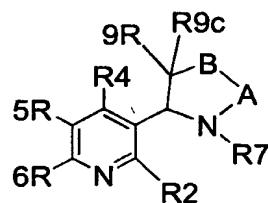


wherein A is 1-6 atoms bridging species linking pyridine and N, B is 1-4 atoms bridging species linking N and Z, Z is H, C₁₋₆alkyl, alkynyl or aryl; R₃ is H or lower alkyl; and R₂, R₄, R₅, and R₆ are H, C₁₋₆alkyl, alkynyl, aryl or S-containing groups.

10

McDonald, et. al., in "Modulators of Acetylcholine Receptors". 1998, U.S. Patent 5,723,477, describe the preparation of C-3 substituted pyridyl compounds and its therapeutic utility. A similar disclosure is made in **McDonald, et. al., 1997**, U.S. Patent 5,703,100; **McDonald, et. al., 1997**, U.S. Patent 5,677,459; **Menzaghi, et. al., 1997**, *J. Pharmacol Exp. Ther.* 280, 373, 384, and 393; and **Lloyd, et. al., 1998**, *Life Sci.*, 62, 1601. Generally, the C-3 substituted pyridyl compounds have the formula:

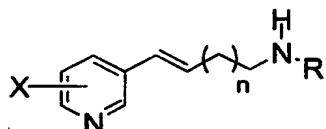
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wherein A is 1-3 atom bridging moiety, forming a 5-7 membered ring; B is -O-, -S-, -NR¹⁰-, -CHR¹⁰-, =CR¹⁰- or =N-; R₂, R₄, R₅ and R₆ are H, C₁₋₆alkyl, aryl, alkynyl, or O-, S-, or N(R)-containing group; and R₇ and R₉ are H, C₁₋₆alkyl, aryl, or alkynyl.

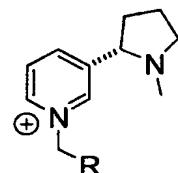
Caldwell, et. al., in "Method for Treatment of Neurodegenerative Diseases" 1993, U.S. Patent 5,212,188, describe the preparation of alkenyl pyridyl compounds and its therapeutic utility. A similar disclosure is made in *Bencherif, et. al.,* 1996 *J. Pharmacol. Exp. Ther.*, 279, 1413 and 1422.

5 Generally, the alkenyl pyridyl compounds have the general formula:



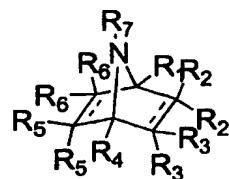
wherein n is 1-5, R is H or C₁₋₅alkyl and X is halogen.

10 *Crooks, et. al.,* in "Nicotinic Receptor Antagonists in the Treatment of Neuropharmacological Disorders" 1997, U.S. Patent 5,691,365, describe the preparation of nicotine analogs and its therapeutic utility. Generally, the nicotinic analogues have the structure:



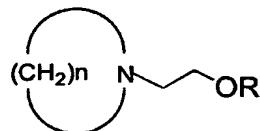
15 wherein R is alkyl or branched alkyl with 2-19 carbon atoms, cycloalkyl, aralkyl or alkenyl.

20 *Shen, et. al.,* in "7-Azabicyclo[2.2.2]-Heptane and -Heptene Derivatives as Cholinergic Receptor Ligands" 1996, W.O. Patent 96/06093, describe the preparation of 7-azabicyclo[2.2.2]-heptane and -heptene derivatives and their therapeutic utilities. A similar disclosure is made by *Shen, et. al.,* 1994, W.O. Patent 94/22868. Generally, the heptane and heptene derivatives have the formula:



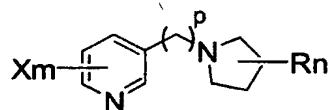
wherein R_1 , R_2 , R_3 , R_4 , R_5 , R_6 , and R_7 are H, alkyl or an alkyl-heteroatom containing group.

5 *Dybes, et. al.*, in "Anticoccidal Cyclicaminoethanols and Esters Thereof" 1978, U.S. Patent 4,094,976, describe the preparation of cyclicaminoethanols and esters and their therapeutic utilities. Generally, the cyclicaminoethanols have the formula:



10 wherein n is 3-5 and R is H or acyl radical.

Caldwell, et. al., in "Method for Treatment of Neurodegenerative Disease" 1993, U.S. Patent 5,214,060 describes the preparation of 3-aminoalkylpyridines and its therapeutic utilities. Generally, the 15 3-aminoalkylpyrimidines have the formula:



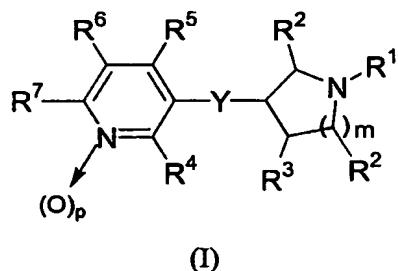
wherein R is C_{1-7} alkyl, X is substituent other than H, p is 1-5, m is 0-4 and n is 0-8.

20 There are two recent reviews on the topic of the nicotinic acetylcholine receptor: *Holladay, et. al.*, in "Neuronal Nicotinic Acetylcholine Receptors as

Targets for Drug Discovery" 1997, *J. Med. Chem.*, 40, 4169; and Holladay, et al., in "Structure-Activity Relationships of Nicotinic Acetylcholine Receptor Agonists as Potential Treatments for Dementia" 1995, *Drug Dev. Res.*, 35, 191.

SUMMARY OF THE INVENTION

5 There are provided by the present invention selective modulators of the nicotinic acetylcholine receptor of the general formula:



wherein

10

m is selected from 0, 1 or 2;

p is selected from 0 or 1;

15 Y is selected from the group consisting of O, S, S(O) and S(O)₂;

R¹ is independently selected from the group consisting of H-, HO-, O-, C₁₋₆alkyl-, C₂₋₆alkenyl-, C₂₋₆alkynyl-, C₃₋₆cycloalkylC₁₋₃alkyl-, phenylC₁₋₃alkyl-, -C(O)C₁₋₆alkyl, -C(O)phenyl, -C(O)C₁₋₆alkylphenyl, -C(O)OC₁₋₆alkyl,

20

-C(O)Ophenyl, -C(O)NHC₁₋₆alkyl, -C(O)N(C₁₋₆alkyl)₂ and -C(O)NHphenyl;

wherein R¹ is optionally substituted on a carbon atom with one to three R^a substituents; wherein R^a is independently selected from the group consisting of C₁₋₄alkyl, C₁₋₄alkoxy, hydroxyC₁₋₄alkyl, carbomethoxy, acetoxy, nitro, Cl, Br and F;

25

R^2 is independently selected from the group consisting of H, C_{1-6} alkyl, phenyl and heteroaryl; wherein heteroaryl is as defined below;

R^3 is selected from the group consisting of H, C_{1-6} alkyl, Cl, Br and F;

5 with the proviso that if m is 0, then R^3 is not Cl, Br or F; and

R^4 , R^5 , R^6 and R^7 are independently selected from the group consisting of hydrogen and selected radicals; wherein the radicals are selected from the group consisting of:

10 a) a trifluoromethyl group: $-CF_3$;

b) a halogen atom: -Br, -Cl, -F or -I;

c) a C_{1-4} alkoxy radical: $-OC_{1-4}$ alkyl; wherein the alkyl is optionally mono- or di-substituted by R^q ; wherein

R^q is selected from the group consisting of -OH, -OCH₃, -CN, -C(O)NH₂, -OC(O)NH₂, CHO, -OC(O)N(CH₃)₂, -SO₂NH₂, SO₂N(CH₃)₂, -SOCH₃, SO₂CH₃, -F, -CF₃, -COOM^a (wherein M^a is selected from the group consisting of hydrogen, alkali metal, methyl and phenyl), tetrazolyl (wherein the point of attachment is the carbon atom of the tetrazole ring and one of the nitrogen atoms is mono-substituted by M^a, as defined previously) and -SO₃M^b (wherein M^b is selected from the group consisting of hydrogen and an alkali metal);

d) a hydroxy group: -OH;

e) a carbonyloxy radical: -O(C=O)R^s; wherein

25 R^s is a group selected from the group consisting of C_{1-4} alkyl, phenyl and heteroaryl (each of which is optionally mono- or di-substituted with R^q , as defined previously); wherein

heteroaryl is a monocyclic aromatic hydrocarbon group having

30 five or six ring atoms, having at least one carbon atom which is the point of attachment, having from one to three carbon atoms replaced by N in the case of six ring atoms, having one carbon atom replaced by O, S or N in the case of five ring

atoms and, optionally, having up to three additional carbon atoms replaced by N;

- f) a carbamoyloxy radical: $-\text{O}(\text{C}=\text{O})\text{N}(\text{R}^y)\text{R}^z$; wherein R^y and R^z are independently selected from the group consisting of H, $\text{C}_{1-4}\text{alkyl}$ (optionally mono- or di-substituted by R^q , as defined previously), a three to five membered diradical to form a ring wherein R^y and R^z are fused (optionally mono- or di-substituted with R^q , as defined previously) and a two to five membered diradical interrupted by $-\text{O}-$, $-\text{S}-$, $-\text{S}(\text{O})-$ or $-\text{S}(\text{O})_2-$ to form a ring wherein R^y and R^z are fused (optionally mono- or di-substituted with R^q , as defined previously);
- g) a sulfur radical: $-(\text{S}=(\text{O})_n)\text{R}^s$; wherein n is selected from 0, 1 or 2 and R^s is as defined previously;
- h) a sulfamoyl group: $-\text{SO}_2\text{N}(\text{R}^y)\text{R}^z$; wherein R^y and R^z are as defined previously;
- i) an azido radical: N_3 ;
- j) a formylamino group: $-(\text{N}-\text{R}^t)-(\text{C}=\text{O})\text{H}$; wherein R^t is selected from the group consisting of H and $\text{C}_{1-4}\text{alkyl}$; wherein the alkyl chain is optionally mono- or di-substituted by R^q , as defined previously;
- k) a $(\text{C}_{1-4}\text{alkyl})\text{carbonylamino}$ radical: $-(\text{N}-\text{R}^t)-(\text{C}=\text{O})-\text{C}_{1-4}\text{alkyl}$; wherein R^t is as defined previously; wherein the alkyl chain is optionally mono- or di-substituted by R^q , as defined previously;
- l) a $(\text{C}_{1-4}\text{alkoxy})\text{carbonylamino}$ radical: $-(\text{N}-\text{R}^t)-(\text{C}=\text{O})-\text{O}-\text{C}_{1-4}\text{alkyl}$; wherein R^t is as defined previously; wherein the alkyl chain is optionally mono-substituted by R^q , as defined previously;
- m) a ureido group: $-(\text{N}-\text{R}^t)-(\text{C}=\text{O})\text{N}(\text{R}^y)\text{R}^z$; wherein R^t , R^y and R^z are as defined previously;
- n) a sulfonamido group: $-(\text{N}-\text{R}^t)\text{SO}_2\text{R}^s$; wherein R^s and R^t are as defined previously;
- o) a cyano group: $-\text{CN}$;

- p) a (C_{1-4} alkyl)carbonyl radical; wherein the carbonyl is acetalized: $-C(OMe)_2C_{1-4}$ alkyl; wherein the alkyl is optionally mono-substituted by R^q , as defined previously;
- 5 q) a carbonyl radical: $-(C=O)R^s$; wherein R^s is as defined previously;
- r) a hydroximinomethyl radical; wherein the oxygen or carbon atom is optionally substituted with a C_{1-4} alkyl group: $-CR^y=NOR^z$; wherein R^y and R^z are as defined previously;
- 10 with the proviso that R^y and R^z may not be joined together to form a ring;
- s) a (C_{1-4} alkoxy)carbonyl radical: $-(C=O)OC_{1-4}$ alkyl; wherein the alkyl is optionally mono- or di-substituted by R^q , as defined previously;
- 15 t) a carbamoyl radical: $-(C=O)N(R^y)R^z$; wherein R^y and R^z are as defined previously;
- u) a N-hydroxycarbamoyl or $N(C_{1-4}$ alkoxy)carbamoyl radical in which the 20 nitrogen atom may additionally be substituted by a C_{1-4} alkyl group: $-(C=O)-N(OR^y)R^z$; wherein R^y and R^z are as defined previously;
- with the proviso that R^y and R^z may not be joined together to form a ring;
- v) a thiocarbamoyl group: $-(C=S)N(R^y)R^z$; wherein R^y and R^z are as defined previously;
- 25 w) a carboxyl radical: $-COOM^b$; wherein M^b is as defined previously;
- x) a thiocyanate radical: $-SCN$;
- y) a trifluoromethylthio radical: $-SCF_3$;
- z) a tetrazolyl radical; wherein the point of attachment is the carbon 30 atom of the tetrazole ring and any one nitrogen atom is mono-substituted by a substituent selected from the group consisting of hydrogen, an alkali metal and a C_{1-4} alkyl radical; wherein the C_{1-4} alkyl radical is optionally mono- or di-substituted by R^q , as defined previously;
- aa) an anionic function selected from the group consisting of phosphono [$P=O(OM^b)_2$], alkylphosphono [$P=O(OM^b)-[O(C_{1-4}$ alkyl)]], alkylphosphinyl [$P=O(OM^b)-(C_{1-4}$ alkyl)], phosphoramido [$P=O(OM^b)N(R^y)R^z$ and $P=O-(OM^b)NHR^y$], sulfino (SO_2M^b), sulfo

(SO₃M^b) and acylsulfonamides selected from the group consisting of CONM^bSO₂R^x, CONM^bSO₂N(R^y)R^z, SO₂NM^bCON(R^y)R^z and SO₂NM^bCN; wherein

R^x is selected from the group consisting of phenyl and heteroaryl;
5 wherein heteroaryl is as defined previously and the phenyl and heteroaryl substituents are optionally mono- or di-substituted with R^q, as defined previously; M^b, R^y and R^z are as defined previously;

ab) a C₅-C₇ cycloalkyl group; wherein any one carbon atom in the ring is replaced by a heteroatom selected from the group consisting of O, S, NH and N(C₁₋₄alkyl); and, in which any one additional carbon atom may be replaced with NH or N(C₁₋₄alkyl) and in which at least one carbon atom adjacent to each nitrogen heteroatom has both of its attached hydrogen atoms replaced by one oxygen whereby a carbonyl moiety is formed;
10 with the proviso that there are at most two carbonyl moieties present in the ring;

ac) a C₂-C₄ alkenyl radical; wherein the radical is optionally mono-substituted by a substituent selected from the group consisting of any one of a) to ab) or is optionally mono-substituted by substituents selected from the group consisting of phenyl, pyridyl, quinoline and isoquinoline; wherein each phenyl, pyridyl, quinoline or isoquinoline substituent is optionally mono- or di-substituted by R^q, as defined previously;
15

ad) a C₁-C₄ alkyl radical;

ae) a C₁-C₄ alkyl mono-substituted by a substituent selected from the group consisting of any one of a) to ad);

af) a 2-oxazolidinonyl moiety; wherein the point of attachment is the nitrogen atom of the oxazolidinone ring; wherein the ring oxygen atom is optionally replaced by a heteroatom selected from the group consisting of S and NR^t (wherein R^t is as defined previously) and one of the saturated carbon atoms of the oxazolidinone ring is optionally
20

30

mono-substituted by a substituent selected from the group consisting of any one of a) to ae);

5 ag) a C₂-C₄ alkynyl radical; wherein the radical is independently selected from the group consisting of any one of a) to af) and trialkylsilyl;

10 ah) phenyl radicals

15 ai) bicyclic radicals; wherein the radical is independently selected from the group consisting of naphthyl, biphenyl, quinoline, indolizine, indole, isoindole, indoline, benzofuran, indazole, benzimidazole, purine, quinolizine, cinnoline, quinoxaline, phthalazine and quinazoline;

20 aj) heterocyclic radicals; wherein the radical is independently selected from the group consisting of furyl, thienyl, pyrazinyl, pyridazinyl, pyrimidinyl, pyrrolyl, pyrazolyl, imidazolyl, indolyl, thiazolyl, oxazolyl, thiadiazolyl, oxadiazolyl, quinolinyl and isoquinolinyl; and

25 ak) aryl and heteroaryl radicals; wherein the radical is independently selected from the group consisting of any one of ah) through aj); wherein the radical is substituted with one to two substituents independently selected from the group consisting of C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ alkoxyC₁-C₆ alkyl, C₁-C₆ alkoxyC₁-C₆ alkoxy, C₁-C₆ thioalkyl, halogen, cyano, hydroxy, amino, nitro and C₁-C₆ alkylamino, in which any terminal carbon atom may be replaced by a group selected from the group consisting of carboxyl and C₂-C₆ alkoxy carbonyl;

and pharmaceutically acceptable salts and esters thereof.

DETAILED DESCRIPTION OF THE INVENTION

30 Relative to the above generic description, certain compounds of the general formula (I) are preferred. Particularly preferred embodiments are those compounds wherein:

5 R¹ is selected from the group consisting of hydrogen, methyl, ethyl, *i*-propyl, *n*-propyl, *i*-butyl, *t*-butyl, *n*-butyl, *t*-pentyl, *n*-pentyl, cyclohexylmethyl, 3-methyl-1-butyn-3-yl, 4-dimethylaminobenzoyl, 2-hydroxymethylbenzoyl, acetyl, *t*-butyloxycarbonyl, ethoxycarbonyl, phenoxy carbonyl, 4-nitrophenoxy carbonyl, 4-methoxyphenoxy carbonyl, 4-carbomethoxyphenoxy carbonyl, 4-methylphenoxy carbonyl, 2,6-dimethylphenoxy carbonyl, 1-acetoxy-1-methyl-ethoxycarbonyl and benzyloxycarbonyl;

10 R² is selected from the group consisting of hydrogen, methyl, ethyl, *i*-propyl, *n*-propyl, *i*-butyl, *t*-butyl, *n*-butyl, *t*-pentyl, *n*-pentyl, phenyl, thiienyl and pyridyl;

15 R³ is selected from the group consisting of hydrogen, Cl, Br, F, methyl, ethyl, *i*-propyl, *n*-propyl, *i*-butyl, *t*-butyl, *n*-butyl, *t*-pentyl and *n*-pentyl; preferably, R³ is hydrogen;

20 R⁴, R⁵, R⁶ and R⁷ are independently selected from the group consisting of hydrogen, -CH₃, -CH₂CH₃, -(CH₂)₃CH₃, -OCH₃, -SCH₃, -tetrazolyl, -COOH, -CH₂CONH₂, -CH₂CH₂SO₃H, -CONH₂, -SO₂NH₂, -SO₃H, -CON(CH₃)₂, -CN, -CH₂CN, -CH₂SCH₃, -CH₂SO₃H, -CH₂SOCH₃, -CH₂SO₂CH₃, -SO₂CH₃, -SOCH₃, -CH₂OCH₃, -N₃, -OCOCNH₂, -OH, -CHO, -CH₂P(O)(OCH₃)OH, -CF₃, CH₂OC(O)NH₂, -CH₂SO₂NH₂, -SCH₂CH₂CN, Br, Cl, F, -SCF₃, -CH₂SCF₃, -SCH₂CF₃, -COCH₃, -CH=NOH, -CONHOH, -C(S)NH₂, -OCOCH₃, -NHCOC₂H₃, -NHCO₂CH₃, -NHCONH₂, -NHSO₂CH₃, -SCN, -CH=CHCHO, -SCH₂CH₂OH, -CH₂OH, -CH=NOCH₂CO₂H, -CO₂CH₂CH₂OH and -SO₂NHCH₂CONH₂; and

25 heteroaryl is selected from the group consisting of pyrrole, pyridine (1N); oxazole, thiazole, oxazine (1N + 1O or 1S); thiadiazole (2N + 1S); furan (1O); thiophene (1S); pyrazole, imidazole, pyrimidine, pyrazine (2N); triazole, triazine (3N); and tetrazole (4N);

and pharmaceutically acceptable salts and esters thereof.

General Synthetic Methods

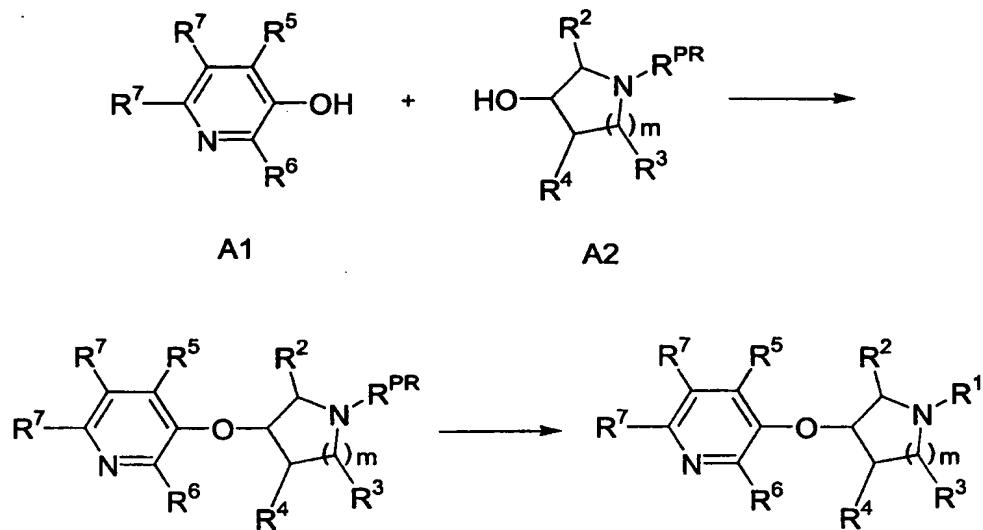
Representative compounds of the present invention can be synthesized in accordance with the general synthetic method schemes described below and are illustrated more particularly in the specific synthetic method schemes that follow. Since the schemes are illustrations, the invention should not be 5 construed as being limited by the chemical reactions and conditions expressed. The preparation of the various starting materials used in the schemes is well within the skill of persons versed in the art.

Compounds of the present invention may be made in a preferred one-step reaction scheme that may be preceded or followed by various 10 processes to obtain the desired substituents R¹ to R⁷ and is followed by deprotection of N-R^{PR} to N-R¹. The preferred one-step reaction is carried out by the conventional procedure known as the Mitsunobu reaction [O. Mitsunobu, *Synthesis*, 1(1981)].

15 Scheme A

Referring to Scheme A, the pyridinyl alcohol Compound A1 is reacted under Mitsunobu conditions with the cyclic alkanol Compound A2 to produce the desired base ring structure of the pyridinyl ethers herein. The reaction takes place in the presence of 1 or 2 equivalents each of triphenylphosphine and either 20 diethyl- or diisopropylazodicarboxylate in a suitable solvent such as benzene, toluene or THF at room temperature to reflux overnight. Subsequently, the protecting group R^{PR} is removed and replaced as desired. Suitable protecting groups include C₁₋₈ substituted or unsubstituted alkyl; such as, methyl, ethyl or propyl; or C₁₋₈ substituted acyl; such as, benzyl carboxylate, allyl carboxylate, 25 acetyl, benzoyl or propanoyl. Many specific protecting groups R^{PR} are included within the definition of R¹. Thus, the end product may conveniently have a substitution with R¹ which was utilized in the synthesis as a nitrogen protecting group. In such case, deprotection is unnecessary.

Scheme A



5

A person skilled in the art can imagine other processes for producing compounds of Formula (I). For example, leaving groups might be employed on analogous starting material Compound A2' wherein the hydroxy on Compound A2' is replaced with with $-OMs$ or $-OTs$ and reacted with Compound A1 to form an ether linkage. The conditions for this reaction are well documented. The thioether linkage; wherein Y is S in Formula (I), can be produced in the manner employing Compound A2' just described using analogous starting material Compound A1', wherein hydroxy is replaced with sulphydryl. The thioether linkage can be oxidized to $S(O)$ or $S(O)_2$ by the use of oxidizing agents such as the peroxides.

The terms used in describing the invention are commonly used and known to those skilled in the art.

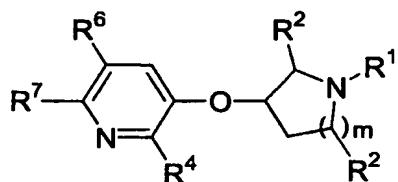
20 With reference to the above definitions, the term "alkyl" refers to a straight or branched chain aliphatic hydrocarbon radical.

The term "pharmaceutically acceptable salts and esters thereof" refers to those salt and ester forms of the compounds of the present invention which would be apparent to the pharmaceutical chemist, i.e., those which are non-toxic and which would favorably affect the pharmacokinetic properties of 5 said compounds of the present invention. Those compounds having favorable pharmacokinetic properties would be apparent to the pharmaceutical chemist, i.e., those which are non-toxic and which possess such pharmacokinetic properties to provide sufficient palatability, absorption, distribution, metabolism and excretion. Other factors, more practical in nature, which are also important 10 in the selection, are cost of raw materials, ease of crystallization, yield, stability, hygroscopicity, and flowability of the resulting bulk drug.

Examples of suitable salts include hydrobromic, hydroiodic, hydrochloric, perchloric, sulfuric, maleic, fumaric, malic, tartaric, citric, benzoic, mandelic, 15 methanesulfonic, hydroethanesulfonic, benzenesulfonic, oxalic, pamoic, 2-naphthalenesulfonic, *p*-toluenesulfonic, cyclohexanesulfamic and saccharic.

Examples of suitable esters include such esters wherein -COOM^a, -COOM^b and -COOH are replaced with *p*-methoxybenzyloxycarbonyl, 20 2,4,6-trimethylbenzyloxycarbonyl, 9-anthryloxycarbonyl, CH₃SCH₂COO-, tetrahydrofur-2-yloxycarbonyl, tetrahydropyran-2-yloxycarbonyl, fur-2-uloxycarbonyl, benzoylmethoxycarbonyl, *p*-nitrobenzyloxycarbonyl, 4-pyridylmethoxycarbonyl, 2,2,2-trichloroethoxycarbonyl, 2,2,2-tribromoethoxycarbonyl, *t*-butyloxycarbonyl, *t*-amyloxycarbonyl, 25 diphenylmethoxycarbonyl, triphenylmethoxycarbonyl, adamantlyloxycarbonyl, 2-benzyloxyphenyloxycarbonyl, 4-methylthiophenyloxycarbonyl or tetrahydropyran-2-yloxycarbonyl.

The preferred compounds of the present invention are listed in Table 1 30 and include compounds of the formula:



wherein R¹ to R⁷ and m are selected concurrently from the group consisting of:

Table 1

Cpd	m	R ¹	R ²	R ⁴	R ⁶	R ⁷
1 ^a	0	H	H	H	H	H
2 ^a	1	CH ₃	H	H	H	H
3 ^a	0	CH ₂ CH ₃	H	H	H	H
4 ^a	0	CH(CH ₃) ₂	H	H	H	H
5 ^a	0	H	H	H	Br	H
6 ^a	0	H	H	H	H	Cl
7 ^a	0	H	H	Cl	H	H
8 ^a	0	H	H	CH ₃	H	H
9 ^a	0	CH ₃	H	H	H	Cl
10 ^a	0	CH ₃	H	H	Br	H
11 ^a	1	H	H	H	H	H
12 ^a	1	CH ₃	H	H	H	H
13 ^a	1	CH ₂ CH ₃	H	H	H	H
14 ^a	1	CH(CH ₃) ₂	H	H	H	H
15 ^a	1	H	H	H	Br	H
16 ^a	1	H	H	CH ₃	H	H
17 ^a	1	H	H	Cl	H	H
18 ^a	1	H	H	Br	H	H
19 ^a	1	CH ₃	H	H	Br	H
20 ^a	1	CH ₃	H	H	H	Cl
21 ^a	1	CH ₃	CH ₃ /CH ₃	H	H	H
22 ^b	1	H	H	H	H	H
23 ^b	1	CH ₃	H	H	H	H

24 ^b	1	CH ₂ CH ₃	H	H	H	H
25 ^b	1	CH(CH ₃) ₂	H	H	H	H
26 ^b	1	H	H	H	Br	H
27 ^b	1	H	H	CH ₃	H	H
28 ^b	1	H	H	Cl	H	H
29 ^b	1	H	H	H	H	CH ₃
30 ^b	1	H	H	H	H	Cl
31 ^b	1	CH ₃	H	H	Br	H
32 ^c	1	H	H	H	H	H
33 ^c	1	CH ₃	H	H	H	H
34 ^c	1	CH ₂ CH ₃	H	H	H	H
35 ^c	1	CH(CH ₃) ₂	H	H	H	H
36 ^c	1	H	H	H	Br	H
37 ^c	1	H	H	CH ₃	H	H
38 ^c	1	H	H	Cl	H	H
39 ^c	1	H	H	H	H	CH ₃
40 ^c	1	H	H	H	H	Cl
41 ^c	1	CH ₃	H	H	Br	H
42 ^b	1	H	H	H	Br	Cl
43 ^b	1	H	H	H	Ph	H
44 ^b	1	H	H	H	(4-CN)Ph	H
45 ^b	1	H	H	H	(3-OMe)Ph	H
46 ^b	1	H	H	H	CCSi(CH ₃) ₃	H
47 ^b	1	H	H	H	CC	H
48 ^b	1	H	H	H	(3-CN)Ph	H
49 ^b	1	H	H	H	(4-OMe)	H
50 ^b	1	H	H	H	(3-Cl)Ph	H
51 ^b	1	H	H	H	(4-F)Ph	H
52 ^b	1	H	H	H	(3-Me)Ph	H
53 ^b	1	H	H	H	(4-SMe)Ph	H
54 ^b	1	H	H	H	(3-F)Ph	H
55 ^b	1	H	H	H	(3-Cl-4-F)Ph	H
56 ^b	1	H	H	H	4-Pyr	H

57 ^b	1	H	H	H	Ph	Cl
58 ^b	1	H	H	H	(4-CN)Ph	Cl
59 ^b	1	H	H	H	(3-OMe)Ph	Cl
60 ^b	1	H	H	H	CCSi(CH ₃) ₃	Cl
61 ^b	1	H	H	H	CC	Cl
62 ^b	1	H	H	H	(3-CN)Ph	Cl
63 ^b	1	H	H	H	(4-OMe)	Cl
64 ^b	1	H	H	H	(3-Cl)Ph	Cl
65 ^b	1	H	H	H	(4-F)Ph	Cl
66 ^b	1	H	H	H	(3-Me)Ph	Cl
67 ^b	1	H	H	H	(4-SMe)Ph	Cl
68 ^b	1	H	H	H	(3-F)Ph	Cl
69 ^b	1	H	H	H	(3-Cl-4-F)Ph	Cl
70 ^b	1	H	<u>H</u>	H	4-Pyr	Cl
71 ^a	2	H	H	H	H	H
72 ^a	2	H	H	Cl	H	H
73 ^a	2	CH ₃	H	H	H	H
74 ^c	2	H	H	H	H	H
75 ^c	2	H	H	Cl	H	H
76 ^c	2	CH ₃	H	H	H	H
77 ^c	2	H	H	H	Br	H
78 ^c	2	CH ₃	H	H	Br	H
79 ^c	2	H	H	H	H	Cl

^a Racemate^b (R)-isomer^c (S)-isomer

Compounds of Formula (I) may be used in pharmaceutical compositions

5 to treat patients (humans and other primates) with disorders related to the modulation of the nicotinic acetylcholine receptor. Thus, the compounds are effective in the treatment of pain, Alzheimer's disease, memory loss/dementia or loss of motor function. The compounds are particularly effective in the treatment of pain.

The preferred route is oral administration, however compounds may be administered by intravenous infusion or topical administration. Oral doses range from about 0.05 mg to about 100 mg, daily. Some compounds of the

5 invention may be orally dosed in the range from about 0.05 mg to about 50 mg daily, while others may be dosed in the range from about 0.05 mg to about 20 mg daily. Infusion doses can range from about 1.0 to about 1.0×10^4 mg/min of inhibitor, admixed with a pharmaceutical carrier over a period ranging from several minutes to several days. For topical administration, compounds of

10 Formula (I) may be mixed with a pharmaceutical carrier at a concentration from about 0.1 % of drug to about 10% of drug to vehicle.

The pharmaceutical compositions can be prepared using conventional pharmaceutical excipients and compounding techniques. Oral dosage forms

15 may be elixirs, syrups, capsules tablets and the like. Where the typical solid carrier is an inert substance such as lactose, starch, glucose, methyl cellulose, magnesium stearate, dicalcium phosphate, mannitol and the like; and typical liquid oral excipients include ethanol, glycerol, water and the like. All excipients may be mixed as needed with disintegrants, diluents, granulating agents,

20 lubricants, binders and the like using conventional techniques known to those skilled in the art of preparing dosage forms. Parenteral dosage forms may be prepared using water or another sterile carrier.

Specific Synthetic Methods

In order to illustrate the invention the following examples are included.

25 These examples do not limit the invention. They are only meant to suggest a method of practicing the invention. Those skilled in the art may find other methods of practicing the invention, which are obvious to them. However those methods are deemed to be within the scope of this invention.

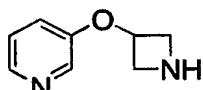
Reagents were purchased from Aldrich, Lancaster, Pfaltz & Bauer, TCI

30 America, and used without further purification. ^1H NMR spectra were collected on a Bruker AC-300 spectrometer. Chemical shifts are reported with respect to

tetramethylsilane (TMS) $\delta_{H,C} = 0.0$ ppm. Spectra were acquired at ambient temperature using DMSO-d₆, CD₃OD or CDCl₃. Mass spectral analyses were performed on a Fisons instrument (Hewlett-Packard HPLC driven electrospray MS instrument). Analytical HPLC analyses were performed on a Hewlett-Packard liquid chromatography system (YMC column, 4 mm x 50 mm, 4 mm C₁₈, 1.0 mL/min, 8 min gradient from 95 % aqueous media (0.1 % TFA) to 95 % CH₃CN (0.1 % TFA), 220 and 260 nm).

Example 1

10



3-(3-Azetidinyl)pyridine

Step (a): 1-t-Butoxycarbonyl-3-hydroxyazetidine

To 2.39 gm (10 mmol) of 1-(diphenylmethyl)-3-hydroxyazetidine in 50 mL of ethanol was added 239 mg of Pd/C. The reaction mixture was then 15 hydrogenated at room temperature for 2 days. After 2 days, the suspension was filtered through celite and washed with H₂O and MeOH. The combined filtrate was concentrated under reduced pressure. To the crude product were then added 50 mL of a solution containing 25 mL of H₂O and 25 mL of dioxane, 2.62 gm (12 mmol) of di-t-butyl dicarbonate, and 2.1 mL (12 mmol) of DIEA at 20 ice-bath temperature. The reaction mixture was slowly warmed to room temperature and allowed to stir at room temperature for 5 h. After 5 h, solvents were removed in vacuo. To the residue were added 100 mL of H₂O and 100 mL of ethyl acetate. After removing the aqueous layer, the organic layer was washed with H₂O (2 x 50 mL) and concentrated under reduced pressure. The 25 crude product was purified by flash chromatography (2 : 1, hexane : ethyl acetate) to obtain 560 mg (32 %) of a clear oil: ¹H NMR (300 MHz, CD₃OD) δ 4.48 (1H, m), 4.10 (2H, t, J = 4.5 Hz), 3.70 (2H, m), 1.43 (9H, s).

Step (b): 3-(1-t-Butoxycarbonyl-3-azetidinyl)pyridine

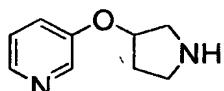
30 To 315 mg (1.2 mmol) of PPh₃ in 5 mL of dry THF at -20°C was added 189 μ L (1.2 mmol) of DEAD dropwise. The solution was allowed to stir 10 min. at -

20°C. After 10 min, a solution containing 173 mg (1 mmol) of N-Boc-3-hydroxyazetidine and 2 mL of dry THF was added dropwise. The solution was again allowed to stir 10 min at -20°C. After 10 min, to the solution was added 95 mg (1 mmol) of 3-hydroxypyridine at once. The solution was then slowly 5 heated to 70°C and allowed to stir at 70°C overnight. Next day, solvent was removed under reduced pressure. The crude product was purified by flash chromatography (2 : 1, Hexane : Ethyl Acetate) to obtain 160 mg (64 % yield) of a yellow oil: ^1H NMR (300 MHz, CD_3OD) δ 8.27 (1H, d, J = 4.8 Hz), 8.18 (1H, d, J = 2.7 Hz), 7.23 (1H, m), 7.05 (1H, m), 4.92 (1H, m), 4.34 - 4.00 (2H, 10 AB, J = 6.6, 9.7 Hz), 1.45 (9H, s).

Step (c): 3-(3-Azetidinyloxy)-pyridine

To 160 mg (0.64 mmol) of 3-(1-t-butoxycarbonyl-3-azetidinyloxy)-pyridine was added 6 mL of solution containing 3 mL of TFA and 3 mL of CH_2Cl_2 at ice-bath 15 temperature. The reaction solution was slowly warmed to room temperature and allowed to stir 50 min at room temperature. After 50 min, solvents were removed in vacuo and the crude product was purified by flash chromatography (9 : 1 : 0.05, CHCl_3 : MeOH : conc. NH_4OH) to obtain 62 mg (67 %) of a white 20 solid: ^1H NMR (300 MHz, CD_3OD) δ 8.23 (2H, br s), 7.38 (2H, br d), 5.24 (2H, br s), 4.58 (2H, br d), 4.20 (2H, br d, J = 9.8 Hz); Mass spectrum (ESI) m/z 151.7 ($\text{M}+\text{H}^+$).

Example 2



3-(3-Pyrrolidinyloxy)-pyridine

25 **Step (a): 1-t-Butoxycarbonyl-3-hydroxypyrrolidine**

To 831 μL (10 mmol) of 3-hydroxypyrrolidine were added 50 mL of a solution containing 25 mL of H_2O and 25 mL of dioxane, 2.62 gm (12 mmol) of di-t-butyl dicarbonate, and 2.1 mL (12 mmol) of DIEA at ice-bath temperature. The reaction mixture was slowly warmed to room temperature and allowed to stir at 30 room temperature for 5 h. After 5 h, solvents were removed in vacuo. To the

residue were added 100 mL of H₂O and 100 mL of ethyl acetate. After removing the aqueous layer, the organic layer was washed with H₂O (2 x 50 mL) and concentrated under reduced pressure. The crude product was purified by flash chromatography (2 : 1, hexane : ethyl acetate) to obtain 1.6 gm (85.6 %) of a clear oil: ¹H NMR (300 MHz, CD₃OD) δ 4.35 (1H, m), 3.41 - 3.25 (4H, m), 1.95 (2H, m), 1.46 (9H, s).

Step (b): 3-(1-t-Butoxycarbonyl-3-pyrrolidinyloxy)-pyridine

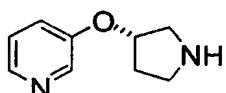
To 755 mg (2.88 mmol) of PPh₃ in 15 mL of dry THF at -20°C was added 453 μL (2.88 mmol) of DEAD dropwise. The solution was allowed to stir 10 min. at -20°C. After 10 min, a solution containing 450 mg (2.4 mmol) of 1-t-butoxycarbonyl-3-hydroxypyrrolidine and 5 mL of dry THF was added dropwise. The solution was again allowed to stir 10 min at -20°C. After 10 min, to the solution was added 229 mg (2.4 mmol) of 3-hydroxypyridine at once. The solution was allowed to stir at room temperature overnight. Next day, solvent was removed under reduced pressure. The crude product was purified by flash chromatography (1 : 4, hexane : ethyl acetate) to obtain 1.3 gm of the product which contained some triphenyl phosphinoxide.

Step (c): 3-(3-Pyrrolidinyloxy)-pyridine

To 1.3 gm of 3-(1-t-butoxycarbonyl-3-pyrrolidinyloxy)-pyridine was added 10 mL of solution containing 5 mL of TFA and 5 mL of CH₂Cl₂ at ice-bath temperature. The reaction solution was slowly warmed to room temperature and allowed to stir 50 min at room temperature. After 50 min, solvents were removed in vacuo and the crude product was purified by flash chromatography (9 : 1 : 0.05, CHCl₃ : MeOH : conc. NH₄OH) to obtain 120 mg (30.4 % yield in two steps) of a clear oil: ¹H NMR (300 MHz, CD₃OD) δ 8.21 (1H, d, J = 2.6 Hz), 8.11 (1H, d, J = 4.7 Hz), 7.38 (2H, m), 5.00 (1H, m), 3.13 - 2.88 (4H, m), 2.20 - 1.95 (2H, m); Mass spectrum (ESI) *m/z* 165.6 (M+H⁺).

30

Example 3

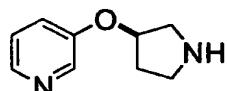


3-(3-(S)-Pyrrolidinyloxy)-pyridine

By the procedure of Example 2, employing the appropriate 3-(R)-hydroxypyrrrolidine in place of 3-hydroxypyrrrolidine, 3-(3-(S)-pyrrolidinyloxy)-pyridine was produced as a clear oil: ^1H NMR (300 MHz, CD_3OD) δ 8.21 (1H, d, J = 2.6 Hz), 8.11 (1H, d, J = 3.6 Hz), 7.43 - 7.34 (2H, m), 5.00 (1H, m), 3.12 - 2.87 (4H, m), 2.20 - 1.92 (2H, m); Mass spectrum (ESI) m/z 165.6 ($\text{M}+\text{H}^+$).

5

Example 4

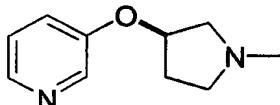


3-(3-(R)-Pyrrolidinyloxy)-pyridine

10 By the procedure of Example 2, employing the appropriate 3-(S)-hydroxypyrrrolidine in place of 3-hydroxypyrrrolidine, 3-(3-(R)-pyrrolidinyloxy)-pyridine was produced as a clear oil: ^1H NMR (300 MHz, CD_3OD) δ 8.21 (1H, d, J = 2.6 Hz), 8.11 (1H, d, J = 4.4 Hz), 7.43 - 7.34 (2H, m), 5.00 (1H, m), 3.13 - 2.89 (4H, m), 2.20 - 1.95 (2H, m); Mass spectrum (ESI) m/z 165.6 ($\text{M}+\text{H}^+$).

15

Example 5



3-(1-Methyl-3-(R)-pyrrolidinyloxy)-pyridine

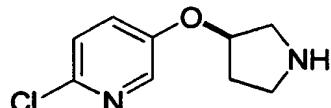
To 164 mg (1 mmol) of 3-(3-(R)-pyrrolidinyloxy)-pyridine were added 300 mg (10 mmol) of paraformaldehyde, 314 mg (5 mmol) of NaCNBH_3 , and 5 mL of dry THF at room temperature. To the suspension was added 2 mL of trifluoroacetic acid dropwise. The suspension was allowed to stir at room temperature overnight. Next day, to the suspension was slowly added a mixture containing 20 mL of 4N NaOH and ice-chips. The mixture was then extracted with ethyl acetate (2 x 40 mL). The combined organic layers were dried over Na_2SO_4 , and concentrated under reduced pressure. The crude product was purified by flash chromatography (15 : 1, CHCl_3 : MeOH) to obtain 9 mg (5 %) of a clear oil: ^1H NMR (300 MHz, CD_3OD) δ 8.19 (1H, d, J = 1.7

20

25

Hz), 8.12 (1H, m), 7.38 (2H, m), 4.99 (1H, m), 2.94 - 2.80 (3H, m), 2.52 - 1.93 (3H, m), 2.40 (3H, s); Mass spectrum (ESI) *m/z* 179.4 (M+H⁺).

Example 6

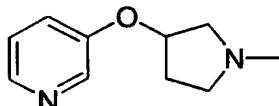


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2-Chloro-5-(3-(R)-pyrrolidinyl)pyridine

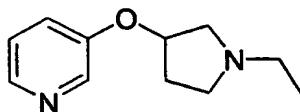
By the procedure of Example 2, employing the appropriate 3-(S)-hydroxypyrrolidine in place of 3-hydroxypyrrolidine and 2-chloro-5-hydroxypyridine in place of 3-hydroxypyridine, 2-chloro-5-(3-(R)-pyrrolidinyl)pyridine was produced as a clear oil: ¹H NMR (300 MHz, CD₃OD) δ 8.10 (1H, s), 7.50 (1H, dd, *J* = 2.3, 8.8 Hz), 7.40 (1H, d, *J* = 8.8 Hz), 5.28 (1H, s), 3.63 - 3.31 (4H, m), 2.34 (2H, m).

Example 7



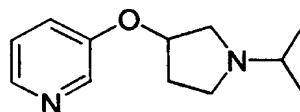
3-(1-Methyl-3-pyrrolidinyl)pyridine

15 To 629 mg (2.4 mmol) of PPh₃ in 13 mL of dry THF at -20°C was added 378 μL (2.4 mmol) of DEAD dropwise. The solution was allowed to stir 10 min. at -20°C. After 10 min, a solution containing 220 μL (2.0 mmol) of 1-methyl-3-hydroxypyrrolidine and 2 mL of dry THF was added dropwise. The solution was again allowed to stir 10 min at -20°C. After 10 min, to the solution was added 190 mg (2.0 mmol) of 3-hydroxypyridine at once. The solution was allowed to stir at room temperature overnight. Next day, solvent was removed under reduced pressure. The crude product was purified by flash chromatography (9 : 1, CHCl₃ : MeOH) to obtain 260 mg (72.9 %) of a clear oil: ¹H NMR (300 MHz, CDCl₃) δ 8.26 (1H, d, *J* = 2.6 Hz), 8.20 (1H, d, *J* = 4.2 Hz), 7.22 - 7.13 (2H, m), 4.85 (1H, m), 2.89 - 2.76 (3H, m), 2.48 - 1.95 (3H, m), 2.40 (3H, s); Mass spectrum (ESI) *m/z* 179.6 (M+H⁺).

Example 8**3-(1-Ethyl-3-pyrrolidinyloxy)-pyridine**

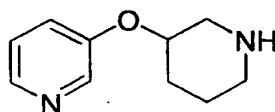
By the procedure of Example 7, employing the appropriate N-ethyl-3-hydroxypyrrolidine in place of N-methyl-3-hydroxypyrrolidine, 3-(1-ethyl-3-pyrrolidinyloxy)-pyridine was produced as a clear oil; ^1H NMR (300 MHz, CDCl_3) δ 8.27 (1H, d, J = 2.6 Hz), 8.20 (1H, d, J = 4.0 Hz), 7.22 - 7.13 (2H, m), 4.87 (1H, m), 2.85 (3H, m), 2.58 - 1.95 (5H, m), 1.14 (3H, t, J = 7.2 Hz); Mass spectrum (ESI) m/z 193.5 ($\text{M}+\text{H}^+$).

10

Example 9**3-(1-Isopropyl-3-pyrrolidinyloxy)-pyridine**

By the procedure of Example 7, employing the appropriate N-isopropyl-3-hydroxypyrrolidine in place of N-methyl-3-hydroxypyrrolidine, 3-(1-isopropyl-3-pyrrolidinyloxy)-pyridine was produced as a light yellow oil; ^1H NMR (300 MHz, CDCl_3) δ 8.26 (1H, d, J = 2.6 Hz), 8.20 (1H, dd, J = 4.3, 1.1 Hz), 7.23 - 7.13 (2H, m), 4.87 (1H, m), 3.08 - 1.97 (7H, m), 1.16 (3H, d, J = 3.4 Hz), 1.14 (3H, d, J = 3.4 Hz); Mass spectrum (ESI) m/z 207.5 ($\text{M}+\text{H}^+$).

20

Example 10**3-(3-Piperidinyloxy)-pyridine**

Step (a): 1-t-Butoxycarbonyl-3-hydroxypiperidine
 To 1.38 gm (10 mmol) of 3-hydroxypyrrolidine were added 50 mL of a solution containing 25 mL of H_2O and 25 mL of dioxane, 2.62 gm (12 mmol) of di-t-butyl dicarbonate, and 2.1 mL (12 mmol) of DIEA at ice-bath temperature. The reaction mixture was slowly warmed to room temperature and allowed to stir at

room temperature for 5 h. After 5 h, solvents were removed in vacuo. To the residue were added 100 mL of H₂O and 100 mL of ethyl acetate. After removing the aqueous layer, the organic layer was washed with H₂O (2 x 50 mL) and concentrated under reduced pressure. The crude product was 5 purified by flash chromatography (1 : 1, hexane : ethyl acetate) to obtain 1.97 gm (98.0 %) of a white solid: ¹H NMR (300 MHz, CD₃OD) δ 3.86 - 3.50 (3H, m), 2.98 - 2.81 (2H, m), 1.92 - 1.73 (2H, m), 1.45 (9H, s), 1.50 - 1.36 (2H, m).

Step (b): 3-(1-t-Butoxycarbonyl-3-piperidinyloxy)-pyridine

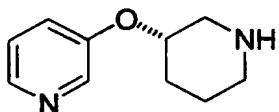
10 To 629 mg (2.4 mmol) of PPh₃ in 13 mL of dry THF at -20°C was added 378 μL (2.4 mmol) of DEAD dropwise. The solution was allowed to stir 10 min. at -20°C. After 10 min, a solution containing 402 mg (2.0 mmol) of 1-t-butoxycarbonyl-3-hydroxypiperidine and 2 mL of dry THF was added dropwise. The solution was again allowed to stir 10 min at -20°C. After 10 min, to the 15 solution was added 190 mg (2.0 mmol) of 3-hydroxypyridine at once. The solution was allowed to stir at room temperature overnight. Next day, solvent was removed under reduced pressure. The crude product was purified by flash chromatography (1 : 1, hexane : ethyl acetate) to obtain 130 gm of the product which contained some triphenyl phosphinoxide.

20

Step (c): 3-(3-Piperidinyloxy)-pyridine

To 130 mg of 3-(1-t-butoxycarbonyl-3-piperidinyloxy)-pyridine was added 10 mL of solution containing 5 mL of TFA and 5 mL of CH₂Cl₂ at ice-bath temperature. The reaction solution was slowly warmed to room temperature 25 and allowed to stir 50 min at room temperature. After 50 min, solvents were removed in vacuo and the crude product was purified by flash chromatography (9 : 1 : 0.05, CHCl₃ : MeOH : conc. NH₄OH) to obtain 83 mg (quantitative yield) of a clear oil: ¹H NMR (300 MHz, CD₃OD) δ 8.27 (1H, d, J = 2.7 Hz), 8.13 (1H, d, J = 4.0 Hz), 7.49 - 7.34 (2H, m), 4.52 (1H, m), 3.20 - 2.80 (4H, m), 2.05 - 30 1.55 (4H, m); Mass spectrum (ESI) *m/z* 179.6 (M+H⁺).

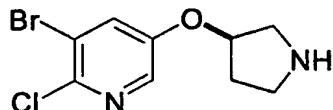
Example 11



3-(3-(S)-Piperidinyloxy)-pyridine

By the procedure of Example 10, employing the appropriate 3-(R)-hydroxypiperidine in place of 3-hydroxypiperidine, 3-(3-(S)-piperidinyloxy)-pyridine was produced as a clear oil: ^1H NMR (300 MHz, CD_3OD) δ 8.27 (1H, d, J = 2.7 Hz), 8.13 (1H, d, J = 4.0 Hz), 7.49 - 7.34 (2H, m), 4.52 (1H, m), 3.20 - 2.80 (4H, m), 2.05 - 1.55 (4H, m); Mass spectrum (ESI) m/z 179.6 ($\text{M}+\text{H}^+$).

Example 12



10 **2-Chloro-3-bromo-5-(3-(R)-pyrrolidinyloxy)-pyridine**

Step (a): *2-Chloro-3-bromo-5-(1-t-butoxycarbonyl 3-(R)-pyrrolidinyloxy)-pyridine*
 To 3.15 gm (12 mmol) of PPh_3 in 100 mL of dry THF at -20°C was added 1.89 mL (12 mmol) of DEAD dropwise. The solution was allowed to stir 10 min. at -20°C. After 10 min, a solution containing 1.87 gm (10 mmol) of 1-t-butoxycarbonyl-3-(R)-hydroxypyrrolidine in 20 mL of dry THF was added dropwise. The solution was again allowed to stir 10 min at -20°C. After 10 min, to the solution was added 2.08 gm (10 mmol) of 2-chloro-3-bromo-5-hydroxypyridine at once. The solution was allowed to stir at room temperature overnight. Next day, solvent was removed under reduced pressure. The crude product was purified by flash chromatography (3 : 1, hexane : ethyl acetate) to obtain 3.65 gm (65 %) of a foamy residue: ^1H NMR (300 MHz, CD_3OD) δ 8.05 (1H, d, J = 2.5 Hz), 7.78 (1H, d, J = 2.5 Hz), 5.09 (1H, s), 3.66 - 3.32 (4H, m), 2.18 (2H, m), 1.46 (9H, s).

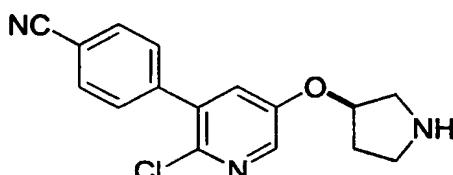
25 **Step (b): 2-Chloro-3-bromo-5-(3-(R)-pyrrolidinyloxy)-pyridine**

By the procedure of Example 2c, employing the appropriate 2-chloro-3-bromo-5-(1-t-butoxycarbonyl 3-(R)-pyrrolidinyloxy)-pyridine, 2-chloro-3-bromo-5-(3-(R)-pyrrolidinyloxy)-pyridine was produced as a clear oil: ^1H NMR (300 MHz,

CD₃OD) δ 8.05 (1H, d, J = 2.5 Hz), 7.77 (1H, d, J = 2.5 Hz), 5.09 (1H, s), 3.63 - 3.31 (4H, m), 2.34 (2H, m).

Example 13

5



2-Chloro-3-(4-cyano)phenyl-5-(3-(R)-pyrrolidinyloxy)-pyridine

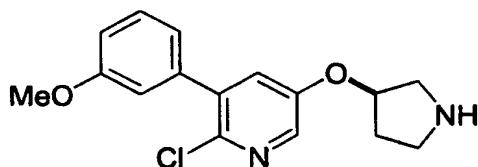
Step (a): 2-Chloro-3-(4-cyano)phenyl-5-(1-t-butoxycarbonyl 3-(R)-pyrrolidinyloxy)-pyridine

To 567 mg (1.5 mmol) of 2-chloro-3-bromo-5-(1-t-butoxycarbonyl 3-(R)-pyrrolidinyloxy)-pyridine and 330 mg (2.25 mmol) of 4-cyanophenylboronic acid were added 6 mL of toluene, 6 mL of absolute ethanol, 1.25 mL of [1M] Na₂CO₃, 63 mg (1.5 mmol) of LiCl and 29 mg (0.025 mmol) of Pd(PPh₃)₄ under N₂ at room temperature. The suspension was slowly heated to 80°C and allowed to stir overnight at 80°C. Next day, supernatants were collected and concentrated in vacuo. The crude product was purified by flash chromatography (5 : 2, hexane : ethyl acetate) to obtain 500 mg (83 %) of a foamy residue.

Step (b): 2-Chloro-3-(4-cyano)phenyl-5-(3-(R)-pyrrolidinyloxy)-pyridine

20 By the procedure of Example 2c, employing 490 mg (1.23 mmol) of the appropriate 2-chloro-3-(4-cyano)phenyl-5-(1-t-butoxycarbonyl 3-(R)-pyrrolidinyloxy)-pyridine, 340 mg (75 %) of 2-chloro-3-(4-cyano)phenyl-5-(3-(R)-pyrrolidinyloxy)-pyridine was produced as a clear oil: ¹H NMR (300 MHz, CD₃OD) δ 8.11 (1H, d, J = 2.9 Hz), 7.84 (2H, d, J = 8.2 Hz), 7.66 (2H, d, J = 8.3 Hz), 7.46 (1H, d, J = 2.9 Hz), 5.07 (1H, s), 3.34 - 2.91 (4H, m), 2.19 - 2.04 (2H, m).

Example 14



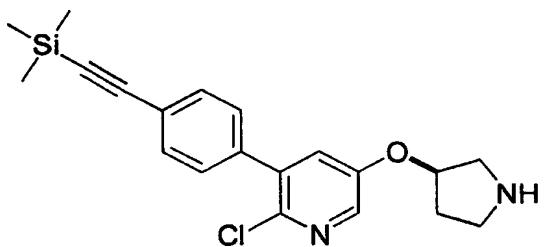
2-Chloro-3-(3-methoxy)phenyl-5-(3-(R)-pyrrolidinyloxy)-pyridine

By the procedure of Example 13, employing 570 mg (1.41 mmol) of the appropriate 2-chloro-3-(3-methoxy)phenyl-5-(1-t-butoxycarbonyl 3-(R)-

5 pyrrolidinyloxy)-pyridine, 380 mg (72 %) of 2-chloro-3-(3-methoxy)phenyl-5-(3-(R)-pyrrolidinyloxy)-pyridine was produced as a clear oil: ^1H NMR (300 MHz, CD_3OD) δ 8.05 (1H, d, J = 2.9 Hz), 7.38 (2H, m), 7.01 (3H, m), 5.06 (1H, s), 3.83 (3H, s), 3.16 - 2.90 (4H, m), 2.21 - 2.03 (2H, m).

10

Example 15



2-Chloro-3-(4-trimethylsilyl ethynyl)phenyl-5-(3-(R)-pyrrolidinyloxy)-pyridine

Step (a): 2-Chloro-3-(4-trimethylsilyl ethynyl)phenyl-5-(1-t-butoxycarbonyl 3-(R)-

15 pyrrolidinyloxy)-pyridine

To 1.68 gm (4.4 mmol) of 2-chloro-3-bromo-5-(1-t-butoxycarbonyl 3-(R)-pyrrolidinyloxy)-pyridine in 45 mL of dry THF were added 4.5 mL of Et_3N , 1.26 mL (8.9 mmol) of trimethylsilylacetylene, 257 mg (0.2 mmol) of $\text{Pd}(\text{PPh}_3)_4$, and 42 mg (0.2 mmol) of CuI at room temperature. The suspension was slowly

20 heated to 70°C and allowed to stir 4 h at 70°C. After 4 h, the suspension was cooled to room temperature and allowed to stir 3 days at room temperature. After 3 days, the crude product was concentrated and purified by flash chromatography (6 : 1, hexane : ethyl acetate) to obtain 1.3 gm (74 %) of a yellow oil: ^1H NMR (300 MHz, CD_3OD) δ 8.03 (1H, s), 7.55 (1H, d, J = 2.8 Hz), 5.07 (1H, s), 3.65 - 3.35 (4H, m), 2.16 - 2.00 (2H, m), 1.46 (9H, s), 0.26 (9H, s).

25

Step (b): 2-Chloro-3-(4-trimethylsilylethynyl)phenyl-5-(3-(R)-pyrrolidinyloxy)-pyridine

By the procedure of Example 2c, employing 650 mg (1.66 mmol) of the appropriate 2-chloro-3-(4-trimethylsilylethynyl)phenyl-5-(1-t-butoxycarbonyl-3-(R)-pyrrolidinyloxy)-pyridine, 380 mg (63 %) of 2-chloro-3-(4-trimethylsilylethynyl)phenyl-5-(3-(R)-pyrrolidinyloxy)-pyridine was produced as a clear oil: ^1H NMR (300 MHz, CD_3OD) δ 8.03 (1H, d, J = 2.9 Hz), 7.55 (1H, d, J = 2.9 Hz), 5.09 (1H, s), 3.34 - 3.11 (4H, m), 2.19 - 2.10 (2H, m), 0.26 (9H, s).

10

Biological Protocols

Example 1

$\alpha_4\beta_2$ nicotinic Acetylcholine Receptor ($\alpha_4\beta_2$ nAChR)

In Vitro Protocol for Determination of $\alpha_4\beta_2$ nAChR Binding Potencies of Ligands

Binding of ^3H -cytisine to neuronal nicotinic acetylcholine receptors was accomplished using crude synaptic membrane preparations from rat cerebral cortex, striatum and hippocampus. Either fresh or frozen membranes were homogenized in ~50 volumes of 10 mM HEPES (N-2-Hydroxyethylpiperazine-N'-2-Ethanesulfonic acid, pH 7.4) and centrifuged at 42,000 x g. The P_2 fraction was resuspended in ~40 volumes of 10 mM HEPES and centrifuged at 42,000 x g. This step was repeated and the P_2 fraction was resuspended in 25 volumes (e.g. 1 g of original into 25 mL) of a medium comprising Na^+ -HEPES buffer (10 mM, pH 7.4), 5 mM MgCl_2 , 0.01% powdered bovine serum albumin (BSA) and 100 mM NaCl . To initiate the binding reaction, test compound (100 μL), Na -HEPES buffered incubation medium (400 μL), ^3H -cytisine (250 μL) and the suspension of biological membranes (250 μL) were mixed, and then the samples were incubated at 23°C for 40 minutes. The binding reaction was terminated by filtration using a Brandel Cell Harvester and the amount of bound ^3H -cytisine for each sample was quantitated using a Wallac LKB 1205 Betaplate liquid scintillation counter. All test compounds were screened at 10 μM in quadruplicate. Nonspecific binding was determined using 10 μM (+)-epibatidine to block all binding of ^3H -cytisine to the $\alpha_4\beta_2$ nAChR. The

activity of each test compound was calculated as follows. After correcting for nonspecific binding, the percent inhibition of specific binding (total binding minus nonspecific) was calculated. Each active compound was further tested at five concentrations to generate a concentration-inhibition curve. The IC_{50} values were determined using the Prism (GraphPad Software) nonlinear regression program.

Example 2

α_7 nicotinic Acetylcholine Receptor (α_7 nAChR)

In Vitro Protocol for Determination of α_7 nAChR Binding Potencies of Ligands

Binding of 3 H-MLA (methylcaconitine) to neuronal nicotinic acetylcholine receptors was accomplished using crude synaptic membrane preparations from rat cerebral cortex, striatum and hippocampus. Either fresh or frozen membranes were homogenized in ~50 volumes of 10 mM HEPES (N-2-Hydroxyethylpiperazine-N'-2-Ethanesulfonic acid, pH 7.4) and centrifuged at 42,000 x g. The P_2 fraction was resuspended in ~40 volumes of 10 mM HEPES and centrifuged at 42,000 x g. This step was repeated and the P_2 fraction was resuspended in 25 volumes (e.g. 1 g of original into 25 mL) of a medium comprised of Na^+ -HEPES buffer (10 mM, pH 7.4), 5 mM $MgCl_2$, 0.01% powdered bovine serum albumin (BSA), and 100 mM NaCl. To initiate the binding reaction, test compound (100 μ L), Na-HEPES buffered incubation medium (400 μ L), 3 H-MLA (250 μ L) and the suspension of biological membranes (250 μ L) were mixed, and then the samples were incubated at 23°C for 40 minutes. The binding reaction was terminated by filtration using a Brandel Cell Harvester, and the amount of bound 3 H-MLA for each sample was quantitated using a Wallac LKB 1205 Betaplate liquid scintillation counter. All test compounds were screened at 10 μ M in quadruplicate. Nonspecific binding was determined using 10 μ M MLA to block all binding of 3 H-MLA to the α_7 nAChR. The activity of each test compound was calculated as follows. After correcting for nonspecific binding, the percent inhibition of specific binding (total binding minus nonspecific) was calculated. Each active compound was further tested at five concentrations to generate a concentration-inhibition

curve. The IC₅₀ values were determined using the Prism (GraphPad Software) nonlinear regression program.

Biological Data

Table 2 provides the test results from the Biological Protocols for the compounds from Examples 1 to 15 provided by the Specific Synthetic Methods.

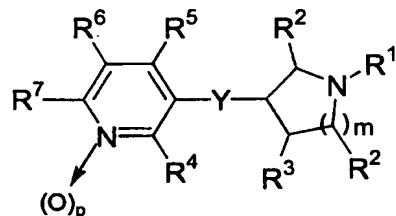
Table 2

Ex #	$\alpha_4\beta_2$ (nM)	α_7 (% Inh @ 10 uM)
1	46 ^a	21
2	209	-15
3	449	5
4	45	11
5	544	20
6	466	20
7	92	22
8	71 ^a	18
9	30 ^a	19
10	204	19
11	673	86
12	94	11
13	22	26
14	58	33
15	25	22

^a % Inhibition at 10 μ M

WHAT IS CLAIMED IS:

1. A compound of the general formula:



wherein

5

m is selected from 0, 1 or 2;

p is selected from 0 or 1;

10 Y is selected from the group consisting of O, S, S(O) and S(O)₂;

R^1 is independently selected from the group consisting of H-, HO-, O-, C₁₋₆alkyl-, C₂₋₈alkenyl-, C₂₋₈alkynyl-, C₃₋₆cycloalkylC₁₋₃alkyl-, phenylC₁₋₃alkyl-, -C(O)C₁₋₆alkyl, -C(O)phenyl, -C(O)C₁₋₆alkylphenyl, -C(O)OC₁₋₆alkyl,

15 -C(O)Ophenyl, -C(O)NHC₁₋₆alkyl, -C(O)N(C₁₋₆alkyl)₂ and -C(O)NHphenyl;

wherein R^1 is optionally substituted on a carbon atom with one to three R^a substituents; wherein R^a is independently selected from the group consisting of C₁₋₄alkyl, C₁₋₄alkoxy, hydroxyC₁₋₄alkyl, carbomethoxy, acetoxy, nitro, Cl, Br and F;

20

R^2 is independently selected from the group consisting of H, C₁₋₆alkyl, phenyl and heteroaryl; wherein heteroaryl is as defined below;

R^3 is selected from the group consisting of H, C₁₋₆alkyl, Cl, Br and F;

25 with the proviso that if m is 0, then R^3 is not Cl, Br or F; and

R⁴, R⁵, R⁶ and R⁷ are independently selected from the group consisting of hydrogen and selected radicals; wherein the radicals are selected from the group consisting of:

- a) a trifluoromethyl group: -CF₃;
- b) a halogen atom: -Br, -Cl, -F or -I;
- c) a C₁₋₄alkoxy radical: -OC₁₋₄alkyl; wherein the alkyl is optionally mono- or di-substituted by R^q; wherein

R^q is selected from the group consisting of -OH, -OCH₃, -CN, -C(O)NH₂, -OC-(O)NH₂, CHO, -OC(O)N(CH₃)₂, -SO₂NH₂, SO₂N(CH₃)₂, -SOCH₃,

SO₂CH₃, -F, -CF₃, -COOM^a (wherein M^a is selected from the group consisting of hydrogen, alkali metal, methyl and phenyl), tetrazolyl (wherein the point of attachment is the carbon atom of the tetrazole ring and one of the nitrogen atoms is mono-substituted by M^a, as defined previously) and -SO₃M^b (wherein M^b is selected from the group consisting of hydrogen and an alkali metal);

- d) a hydroxy group: -OH;
- e) a carbonyloxy radical: -O(C=O)R^s; wherein

R^s is a group selected from the group consisting of C₁₋₄alkyl, phenyl and heteroaryl (each of which is optionally mono- or di-substituted with

R^q, as defined previously);

wherein

heteroaryl is a monocyclic aromatic hydrocarbon group having five or six ring atoms, having at least one carbon atom which is the point of attachment, having from one to three carbon atoms replaced

by N in the case of six ring atoms, having one carbon atom replaced by O, S or N in the case of five ring atoms and, optionally, having up to three additional carbon atoms replaced by N;

- f) a carbamoyloxy radical: -O(C=O)N(R^y)R^z; wherein

R^y and R^z are independently selected from the group consisting of H, C₁₋₄alkyl (optionally mono- or di-substituted by R^q, as defined previously), a three to five membered diradical to form a ring wherein R^y and R^z are fused (optionally mono- or di-substituted with R^q, as

defined previously) and a two to five membered diradical interrupted by -O-, -S-, -S(O)- or -S(O)₂- to form a ring wherein R^y and R^z are fused (optionally mono- or di-substituted with R^q, as defined previously);

5 g) a sulfur radical: -(S=(O)_n)-R^s; wherein n is selected from 0, 1 or 2 and R^s is as defined previously;

h) a sulfamoyl group: -SO₂N(R^y)R^z; wherein R^y and R^z are as defined previously;

i) an azido radical: N₃;

10 j) a formylamino group: -(N-R^t)-(C=O)H; wherein R^t is selected from the group consisting of H and C₁₋₄alkyl; wherein the alkyl chain is optionally mono- or di-substituted by R^q, as defined previously;

k) a (C₁₋₄alkyl)carbonylamino radical: -(N-R^t)-(C=O)-C₁₋₄alkyl; wherein 15 R^t is as defined previously, wherein the alkyl chain is optionally mono- or di-substituted by R^q, as defined previously;

l) a (C₁₋₄alkoxy)carbonylamino radical: -(N-R^t)-(C=O)-O-C₁₋₄alkyl; wherein R^t is as defined previously; wherein the alkyl chain is optionally mono-substituted by R^q, as defined previously;

20 m) a ureido group: -(N-R^t)-(C=O)N(R^y)R^z; wherein R^t, R^y and R^z are as defined previously;

n) a sulfonamido group: -(N-R^t)SO₂R^s; wherein R^s and R^t are as defined previously;

o) a cyano group: -CN;

25 p) a (C₁₋₄alkyl)carbonyl radical; wherein the carbonyl is acetalized: -C(OMe)₂C₁₋₄ alkyl; wherein the alkyl is optionally mono-substituted by R^q, as defined previously;

q) a carbonyl radical: -(C=O)R^s; wherein R^s is as defined previously;

r) a hydroximinomethyl radical; wherein the oxygen or carbon atom is 30 optionally substituted with a C₁₋₄alkyl group: -CR^y=NOR^z; wherein R^y and R^z are as defined previously;

with the proviso that R^y and R^z may not be joined together to form a ring;

- s) a (C₁₋₄alkoxy)carbonyl radical: -(C=O)OC₁₋₄alkyl; wherein the alkyl is optionally mono- or di-substituted by R^q, as defined previously;
- t) a carbamoyl radical: -(C=O)N(R^y)R^z; wherein R^y and R^z are as defined previously;
- 5 u) a N-hydroxycarbamoyl or N(C₁₋₄alkoxy)carbamoyl radical in which the nitrogen atom may additionally be substituted by a C₁₋₄alkyl group: -(C=O)-N(OR^y)R^z; wherein R^y and R^z are as defined previously; with the proviso that R^y and R^z may not be joined together to form a ring;
- 10 v) a thiocarbamoyl group: -(C=S)N(R^y)R^z; wherein R^y and R^z are as defined previously;
- w) a carboxyl radical: -COOM^b; wherein M^b is as defined previously;
- x) a thiocyanate radical: -SCN;
- y) a trifluoromethylthio radical: -SCF₃;
- 15 z) a tetrazolyl radical; wherein the point of attachment is the carbon atom of the tetrazole ring and any one nitrogen atom is mono-substituted by a substituent selected from the group consisting of hydrogen, an alkali metal and a C₁₋₄alkyl radical; wherein the C₁₋₄alkyl radical is optionally mono- or di-substituted by R^q, as defined previously;
- 20 aa) an anionic function selected from the group consisting of phosphono [P=O(OM^b)₂], alkylphosphono [P=O(OM^b)-[O(C₁₋₄alkyl)]], alkylphosphinyl [P=O(OM^b)-(C₁₋₄alkyl)], phosphoramido [P=O(OM^b)N(R^y)R^z and P=O-(OM^b)NHR^x], sulfino (SO₂M^b), sulfo (SO₃M^b) and acylsulfonamides selected from the group consisting of CONM^bSO₂R^x, CONM^bSO₂N(R^y)R^z, SO₂NM^bCON(R^y)R^z and SO₂NM^bCN; wherein
- 25 R^x is selected from the group consisting of phenyl and heteroaryl; wherein heteroaryl is as defined previously and the phenyl and heteroaryl substituents are optionally mono- or di-substituted with R^q, as defined previously; M^b, R^y and R^z are as defined previously;
- 30 ab) a C₅-C₇ cycloalkyl group; wherein any one carbon atom in the ring is replaced by a heteroatom selected from the group consisting of O, S, NH and N(C₁₋₄alkyl); and, in which one additional carbon atom may be replaced with NH or N(C₁₋₄alkyl) and in which at least one carbon atom

adjacent to each nitrogen heteroatom has both of its attached hydrogen atoms replaced by one oxygen whereby a carbonyl moiety is formed; with the proviso that there are at most two carbonyl moieties present in the ring;

5 ac) a C₂-C₄ alkenyl radical; wherein the radical is optionally mono-substituted by a substituent selected from the group consisting of any one of a) to ab) or is optionally mono-substituted by substituents selected from the group consisting of phenyl, pyridyl, quinoline and isoquinoline; wherein each phenyl, pyridyl, quinoline or isoquinoline substituent is optionally mono- or di-substituted by R^a, as defined previously;

10 ad) a C₁-C₄ alkyl radical;

 ae) a C₁-C₄ alkyl mono-substituted by a substituent selected from the group consisting of any one of a) to ad);

15 af) a 2-oxazolidinonyl moiety; wherein the point of attachment is the nitrogen atom of the oxazolidinone ring; wherein the ring oxygen atom is optionally replaced by a heteroatom selected from the group consisting of S and NR^t (wherein R^t is as defined previously) and one of the saturated carbon atoms of the oxazolidinone ring is optionally mono-substituted by a substituent selected from the group consisting of any one of a) to ae);

20 ag) a C₂-C₄ alkynyl radical; wherein the radical is independently selected from the group consisting of any one of a) to af) and trialkylsilyl;

 ah) phenyl radicals

25 ai) bicyclic radicals; wherein the radical is independently selected from the group consisting of naphthyl, biphenyl, quinoline, indolizine, indole, isoindole, indoline, benzofuran, indazole, benzimidazole, purine, quinolizine, cinnoline, quinoxaline, phthalazine and quinazoline;

 aj) heterocyclic radicals; wherein the radical is independently selected from the group consisting of furyl, thienyl, pyrazinyl, pyridazinyl, pyrimidinyl, pyrrolyl, pyrazolyl, imidazolyl, indolyl, thiazolyl, oxazolyl, thiadiazolyl, oxadiazolyl, quinolinyl and isoquinolinyl; and

ak) aryl and heteroaryl radicals; wherein the radical is independently selected from the group consisting of any one of ah) through aj); wherein the radical is substituted with one or two substituents independently selected from the group consisting of C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆alkoxyC₁-C₆alkyl, C₁-C₆alkoxyC₁-C₆alkoxy, C₁-C₆ thioalkyl, halogen, cyano, hydroxy, amino, nitro and C₁-C₆alkylamino, in which any terminal carbon atom may be replaced by a group selected from the group consisting of carboxyl and C₂-C₆alkoxycarbonyl;

10 and pharmaceutically acceptable salts and esters thereof.

2. The compound of claim 1 wherein the compound is a selective modulator of the nicotinic acetylcholine receptor.

3. The compound of claim 1 wherein the compound is an antagonist of the 15 nicotinic acetylcholine receptor.

4. The compound of claim 1 wherein the compound is an agonist of the nicotinic acetylcholine receptor.

5. The compound of claim 1 wherein R¹ is selected from the group consisting of hydrogen, methyl, ethyl, *i*-propyl, *n*-propyl, *i*-butyl, *t*-butyl, *n*-butyl, *t*-pentyl, *n*-pentyl, cyclohexylmethyl, 20 3-methyl-1-butyn-3-yl, 4-dimethylaminobenzoyl, 2-hydroxymethylbenzoyl, acetyl, *t*-butyloxycarbonyl, ethoxycarbonyl, phenoxy carbonyl, 4-nitrophenoxy carbonyl, 4-methoxyphenoxy carbonyl, 4-carbomethoxyphenoxy carbonyl, 4-methylphenoxy carbonyl, 25 2,6-dimethylphenoxy carbonyl, 1-acetoxy-1-methyl-ethoxycarbonyl and benzyloxycarbonyl.

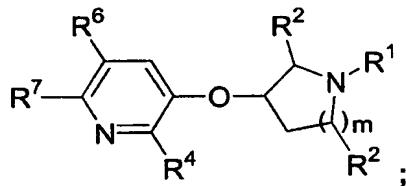
6. The compound of claim 1 wherein

R^2 is selected from the group consisting of hydrogen, methyl, ethyl, *i*-propyl, *n*-propyl, *i*-butyl, *t*-butyl, *n*-butyl, *t*-pentyl, *n*-pentyl, phenyl, thienyl and pyridyl.

7. The compound of claim 1 wherein
5 R^3 is selected from the group consisting of hydrogen, Cl, Br, F, methyl, ethyl, *i*-propyl, *n*-propyl, *i*-butyl, *t*-butyl, *n*-butyl, *t*-pentyl and *n*-pentyl.
8. The compound of claim 1 wherein R^3 is hydrogen.
9. The compound of claim 1 wherein
10 R^4 , R^5 , R^6 and R^7 are independently selected from the group consisting of hydrogen, $-CH_3$, $-CH_2CH_3$, $-(CH_2)_3CH_3$, $-OCH_3$, $-SCH_3$, -tetrazolyl, $-COOH$, $-CH_2CONH_2$, $-CH_2CH_2SO_3H$, $-CONH_2$, $-SO_2NH_2$, $-SO_3H$, $-CON(CH_3)_2$, $-CN$, $-CH_2CN$, $-CH_2SCH_3$, $-CH_2SO_3H$, $-CH_2SOCH_3$, $-CH_2SO_2CH_3$, $-SO_2CH_3$, $-SOCH_3$, $-CH_2OCH_3$, $-N_3$, $-OCOCNH_2$, $-OH$, $-CHO$, $-CH_2P(O)(OCH_3)OH$,
15 $-CF_3$, $CH_2OC(O)NH_2$, $-CH_2SO_2NH_2$, $-SCH_2CH_2CN$, Br, Cl, F, $-SCF_3$, $-CH_2SCF_3$, $-SCH_2CF_3$, $-COCH_3$, $-CH=NOH$, $-CONHOH$, $-C(S)NH_2$, $-OCOCH_3$, $-NHCOCH_3$, $-NHCO_2CH_3$, $-NHCONH_2$, $-NHSO_2CH_3$, $-SCN$, $-CH=CHCHO$, $-SCH_2CH_2OH$, $-CH_2OH$, $-CH=NOCH_2CO_2H$, $-CO_2CH_2CH_2OH$ and $-SO_2NHCH_2CONH_2$.
- 20 10. The compound of claim 1 wherein heteroaryl is selected from the group consisting of pyrrole, pyridine, oxazole, thiazole, oxazine, thiadiazole, furan, thiophene, pyrazole, imidazole, pyrimidine, pyrazine, triazole, triazine and tetrazole.
11. The compound of claim 1 wherein said pharmaceutically acceptable salt
25 is selected from the group consisting of hydrobromic, hydroiodic, hydrochloric, perchloric, sulfuric, maleic, fumaric, malic, tartaric, citric, benzoic, mandelic, methanesulfonic, hydroethanesulfonic, benzenesulfonic, oxalic, pamoic, 2-naphthalenesulfonic, *p*-toluenesulfonic, cyclohexanesulfamic and saccharic.

12. The compound of claim 1 wherein the pharmaceutically acceptable ester is an ester wherein -COOM^a, -COOM^b and -COOH are selected from the group consisting of *p*-methoxybenzyloxycarbonyl, 2,4,6-trimethylbenzyloxycarbonyl, 9-anthryloxycarbonyl, CH₃SCH₂COO-, tetrahydrofur-2-yloxycarbonyl, tetrahydropyran-2-yloxycarbonyl, fur-2-uloxycarbonyl, benzoylmethoxycarbonyl, *p*-nitrobenzyloxycarbonyl, 4-pyridylmethoxycarbonyl, 2,2,2-trichloroethoxycarbonyl, 2,2,2-tribromoethoxycarbonyl, *t*-butyloxycarbonyl, *t*-amyloxycarbonyl, diphenylmethoxycarbonyl, triphenylmethoxycarbonyl, adamantlyloxycarbonyl, 2-benzyloxyphenyloxycarbonyl, 4-methylthiophenyloxycarbonyl or tetrahydropyran-2-yloxycarbonyl.

13. The compound of claim 1 wherein the compound has the general formula:



15 wherein R¹ to R⁷ and m are selected concurrently from the group consisting of:

Cpd	m	R ¹	R ²	R ⁴	R ⁶	R ⁷
1 ^a	0	H	H	H	H	H
2 ^a	1	CH ₃	H	H	H	H
3 ^a	0	CH ₂ CH ₃	H	H	H	H
4 ^a	0	CH(CH ₃) ₂	H	H	H	H
5 ^a	0	H	H	H	Br	H
6 ^a	0	H	H	H	H	Cl
7 ^a	0	H	H	Cl	H	H
8 ^a	0	H	H	CH ₃	H	H

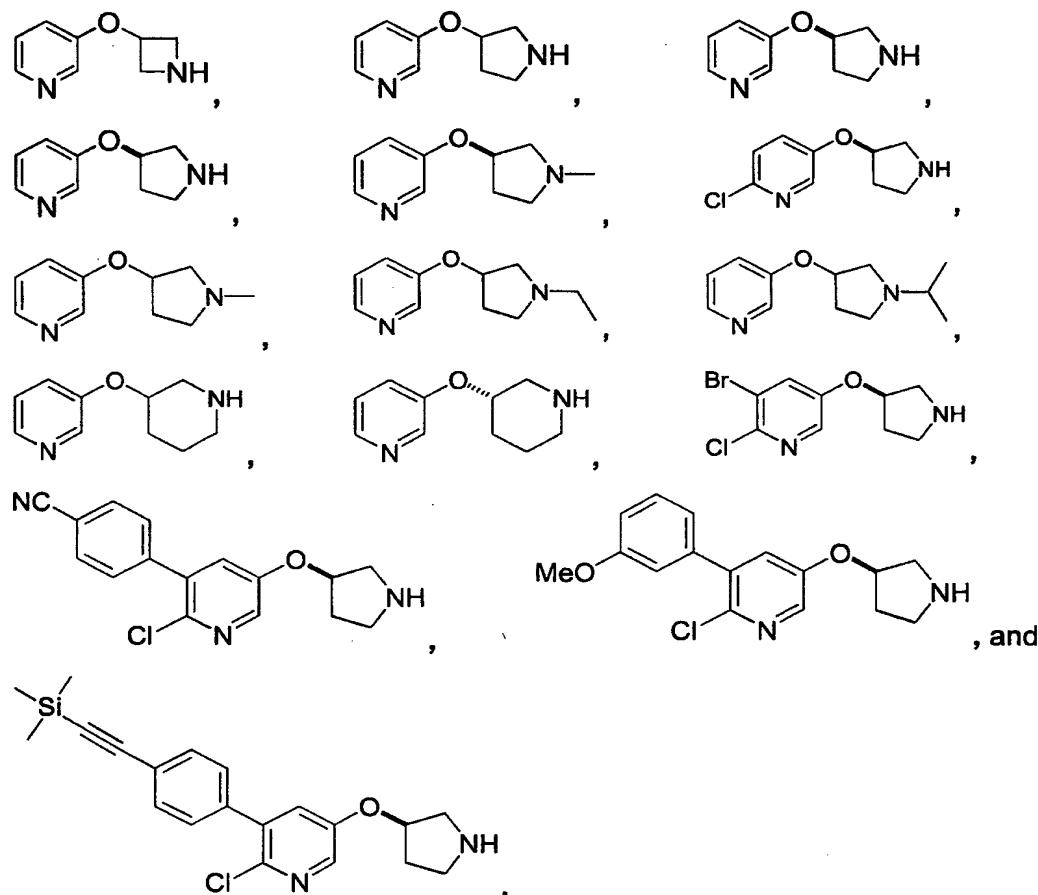
9 ^a	0	CH ₃	H	H	H	Cl
10 ^a	0	CH ₃	H	H	Br	H
11 ^a	1	H	H	H	H	H
12 ^a	1	CH ₃	H	H	H	H
13 ^a	1	CH ₂ CH ₃	H	H	H	H
14 ^a	1	CH(CH ₃) ₂	H	H	H	H
15 ^a	1	H	H	H	Br	H
16 ^a	1	H	H	CH ₃	H	H
17 ^a	1	H	H	Cl	H	H
18 ^a	1	H	H	Br	H	H
19 ^a	1	CH ₃	H	H	Br	H
20 ^a	1	CH ₃	H	H	H	Cl
21 ^a	1	CH ₃	CH ₃ /CH ₃	H	H	H
22 ^b	1	H	H	H	H	H
23 ^b	1	CH ₃	H	H	H	H
24 ^b	1	CH ₂ CH ₃	H	H	H	H
25 ^b	1	CH(CH ₃) ₂	H	H	H	H
26 ^b	1	H	H	H	Br	H
27 ^b	1	H	H	CH ₃	H	H
28 ^b	1	H	H	Cl	H	H
29 ^b	1	H	H	H	H	CH ₃
30 ^b	1	H	H	H	H	Cl
31 ^b	1	CH ₃	H	H	Br	H
32 ^c	1	H	H	H	H	H
33 ^c	1	CH ₃	H	H	H	H
34 ^c	1	CH ₂ CH ₃	H	H	H	H
35 ^c	1	CH(CH ₃) ₂	H	H	H	H
36 ^c	1	H	H	H	Br	H
37 ^c	1	H	H	CH ₃	H	H
38 ^c	1	H	H	Cl	H	H
39 ^c	1	H	H	H	H	CH ₃
40 ^c	1	H	H	H	H	Cl
41 ^c	1	CH ₃	H	H	Br	H

42 ^b	1	H	H	H	Br	Cl
43 ^b	1	H	H	H	Ph	H
44 ^b	1	H	H	H	(4-CN)Ph	H
45 ^b	1	H	H	H	(3-OMe)Ph	H
46 ^b	1	H	H	H	CCSi(CH ₃) ₃	H
47 ^b	1	H	H	H	CC	H
48 ^b	1	H	H	H	(3-CN)Ph	H
49 ^b	1	H	H	H	(4-OMe)	H
50 ^b	1	H	H	H	(3-Cl)Ph	H
51 ^b	1	H	H	H	(4-F)Ph	H
52 ^b	1	H	H	H	(3-Me)Ph	H
53 ^b	1	H	H	H	(4-SMe)Ph	H
54 ^b	1	H	H	H	(3-F)Ph	H
55 ^b	1	H	H	H	(3-Cl-4-F)Ph	H
56 ^b	1	H	H	H	4-Pyr	H
57 ^b	1	H	H	H	Ph	Cl
58 ^b	1	H	H	H	(4-CN)Ph	Cl
59 ^b	1	H	H	H	(3-OMe)Ph	Cl
60 ^b	1	H	H	H	CCSi(CH ₃) ₃	Cl
61 ^b	1	H	H	H	CC	Cl
62 ^b	1	H	H	H	(3-CN)Ph	Cl
63 ^b	1	H	H	H	(4-OMe)	Cl
64 ^b	1	H	H	H	(3-Cl)Ph	Cl
65 ^b	1	H	H	H	(4-F)Ph	Cl
66 ^b	1	H	H	H	(3-Me)Ph	Cl
67 ^b	1	H	H	H	(4-SMe)Ph	Cl
68 ^b	1	H	H	H	(3-F)Ph	Cl
69 ^b	1	H	H	H	(3-Cl-4-F)Ph	Cl
70 ^b	1	H	H	H	4-Pyr	Cl
71 ^a	2	H	H	H	H	H
72 ^a	2	H	H	Cl	H	H
73 ^a	2	CH ₃	H	H	H	H
74 ^c	2	H	H	H	H	H

75 ^c	2	H	H	Cl	H	H
76 ^c	2	CH ₃	H	H	H	H
77 ^c	2	H	H	H	Br	H
78 ^c	2	CH ₃	H	H	Br	H
79 ^c	2	H	H	H	H	Cl

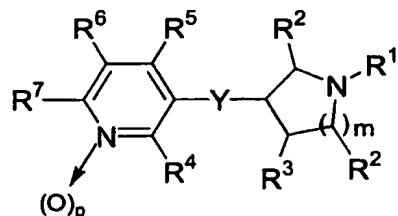
^a Racemate^b (R)-isomer^c (S)-isomer

14. The compound of claim 1 wherein the compound is selected from the
5 group consisting of:



15. A method for treating a condition or disease the pathogenesis of which
may be regulated by modulation of the nicotinic acetylcholine receptor

which comprises the step of administering to a patient suffering from such a condition or disease an effective amount of a compound of the general formula:



5 wherein

m is selected from 0, 1 or 2;

10 p is selected from 0 or 1;

15 Y is selected from the group consisting of O, S, S(O) and S(O)₂;

20 R¹ is independently selected from the group consisting of H-, HO-, O-, C₁₋₆alkyl-, C₂₋₆alkenyl-, C₂₋₆alkynyl-, C₃₋₈cycloalkylC₁₋₃alkyl-, phenylC₁₋₃alkyl-, -C(O)C₁₋₆alkyl, -C(O)phenyl, -C(O)C₁₋₆alkylphenyl, -C(O)OC₁₋₆alkyl, -C(O)Ophenyl, -C(O)NHC₁₋₆alkyl, -C(O)N(C₁₋₆alkyl)₂ and -C(O)NHphenyl; wherein R¹ is optionally substituted on a carbon atom with one to three R^a substituents; wherein R^a is independently selected from the group consisting of C₁₋₄alkyl, C₁₋₄alkoxy, hydroxyC₁₋₄alkyl, carbomethoxy, acetoxy, nitro, Cl, Br and F;

25 R² is independently selected from the group consisting of H, C₁₋₆alkyl, phenyl and heteroaryl; wherein heteroaryl is as defined below;

25 R³ is selected from the group consisting of H, C₁₋₆alkyl, Cl, Br and F; with the proviso that if m is 0, then R³ is not Cl, Br or F; and

R^4 , R^5 , R^6 and R^7 are independently selected from the group consisting of hydrogen and selected radicals; wherein the radicals are selected from the group consisting of:

- 5 a) a trifluoromethyl group: $-CF_3$;
- b) a halogen atom: $-Br$, $-Cl$, $-F$ or $-I$;
- c) a C_{1-4} alkoxy radical: $-OC_{1-4}$ alkyl; wherein the alkyl is optionally mono- or di-substituted by R^q ; wherein

R^q is selected from the group consisting of $-OH$, $-OCH_3$, $-CN$, $-C(O)NH_2$, $-OC(O)NH_2$, CHO , $-OC(O)N(CH_3)_2$, $-SO_2NH_2$, $SO_2N(CH_3)_2$, $-SOCH_3$, SO_2CH_3 , $-F$, $-CF_3$, $-COOM^a$ (wherein M^a is selected from the group consisting of hydrogen, alkali metal, methyl and phenyl), tetrazolyl (wherein the point of attachment is the carbon atom of the tetrazole ring and one of the nitrogen atoms is mono-substituted by M^a , as defined previously) and $-SO_3M^b$ (wherein M^b is selected from the group consisting of hydrogen and an alkali metal);

- d) a hydroxy group: $-OH$;
- e) a carbonyloxy radical: $-O(C=O)R^s$; wherein

R^s is a group selected from the group consisting of C_{1-4} alkyl, phenyl and heteroaryl (each of which is optionally mono- or di-substituted with R^q , as defined previously);

20 wherein

heteroaryl is a monocyclic aromatic hydrocarbon group having five or six ring atoms, having at least one carbon atom which is the point of attachment; having from one to three carbon atoms replaced by N in the case of six ring atoms, having one carbon atom replaced by O, S or N in the case of five ring atoms and, optionally, having up to three additional carbon atoms replaced by N;

- 25 f) a carbamoyloxy radical: $-O(C=O)N(R^y)R^z$; wherein

R^y and R^z are independently selected from the group consisting of H, C_{1-4} alkyl (optionally mono- or di-substituted by R^q , as defined previously), a three to five membered diradical to form a ring

wherein R^y and R^z are fused (optionally mono- or di-substituted with R^q, as defined previously) and a two to five membered diradical interrupted by -O-, -S-, -S(O)- or -S(O)₂- to form a ring wherein R^y and R^z are fused (optionally mono- or di-substituted with R^q, as defined previously);

5 g) a sulfur radical: -(S=(O)_n)-R^s; wherein n is selected from 0, 1 or 2 and R^s is as defined previously;

h) a sulfamoyl group: -SO₂N(R^y)R^z; wherein R^y and R^z are as defined previously;

10 i) an azido radical: N₃;

j) a formylamino group: -(N-R^t)-(C=O)H; wherein R^t is selected from the group consisting of H and C₁₋₄alkyl; wherein the alkyl chain is optionally mono- or di-substituted by R^q, as defined previously;

15 k) a (C₁₋₄alkyl)carbonylamino radical: -(N-R^t)-(C=O)-C₁₋₄alkyl; wherein R^t is as defined previously; wherein the alkyl chain is optionally mono- or di-substituted by R^q, as defined previously;

l) a (C₁₋₄alkoxy)carbonylamino radical: -(N-R^t)-(C=O)-O-C₁₋₄alkyl; wherein

20 R^t is as defined previously; wherein the alkyl chain is optionally mono-substituted by R^q, as defined previously;

m) a ureido group: -(N-R^t)-(C=O)N(R^y)R^z; wherein R^t, R^y and R^z are as defined previously;

n) a sulfonamido group: -(N-R^t)SO₂R^s; wherein R^s and R^t are as defined previously;

25 o) a cyano group: -CN;

p) a (C₁₋₄alkyl)carbonyl radical; wherein the carbonyl is acetalized: -C(OMe)₂C₁₋₄ alkyl; wherein the alkyl is optionally mono-substituted by R^q, as defined previously;

q) a carbonyl radical: -(C=O)R^s; wherein R^s is as defined previously;

30 r) a hydroximinomethyl radical; wherein the oxygen or carbon atom is optionally substituted with a C₁₋₄alkyl group: -CR^y=NOR^z; wherein R^y and R^z are as defined previously;

with the proviso that R^y and R^z may not be joined together to form a ring;

5 s) a (C_{1-4} alkoxy)carbonyl radical: $-(C=O)OC_{1-4}\text{alkyl}$; wherein the alkyl is optionally mono- or di-substituted by R^q , as defined previously;

10 t) a carbamoyl radical: $-(C=O)N(R^y)R^z$; wherein R^y and R^z are as defined previously;

15 u) a N-hydroxycarbamoyl or $N(C_{1-4}\text{alkoxy})\text{carbamoyl}$ radical in which the nitrogen atom may additionally be substituted by a $C_{1-4}\text{alkyl}$ group: $-(C=O)-N(OR^y)R^z$; wherein R^y and R^z are as defined previously;

20 with the proviso that R^y and R^z may not be joined together to form a ring;

25 v) a thiocarbamoyl group: $-(C=S)N(R^y)R^z$; wherein R^y and R^z are as defined previously;

30 w) a carboxyl radical: $-COOM^b$; wherein M^b is as defined previously;

15 x) a thiocyanate radical: $-SCN$;

15 y) a trifluoromethylthio radical: $-SCF_3$;

20 z) a tetrazolyl radical; wherein the point of attachment is the carbon atom of the tetrazole ring and any one nitrogen atom is mono-substituted by a substituent selected from the group consisting of hydrogen, an alkali metal and a $C_{1-4}\text{alkyl}$ radical; wherein the $C_{1-4}\text{alkyl}$ radical is optionally mono- or di-substituted by R^q , as defined previously;

25 aa) an anionic function selected from the group consisting of phosphono [$P=O(OM^b)_2$], alkylphosphono [$P=O(OM^b)-[O(C_{1-4}\text{alkyl})]$], alkylphosphinyl [$P=O(OM^b)-(C_{1-4}\text{alkyl})$], phosphoramido [$P=O(OM^b)N(R^y)R^z$ and $P=O-(OM^b)NHR^x$], sulfino (SO_2M^b), sulfo (SO_3M^b) and acylsulfonamides selected from the group consisting of $CONM^bSO_2R^x$, $CONM^bSO_2N(R^y)R^z$, $SO_2NM^bCON(R^y)R^z$ and SO_2NM^bCN ; wherein

30 R^x is selected from the group consisting of phenyl and heteroaryl; wherein heteroaryl is as defined previously and the phenyl and heteroaryl substituents are optionally mono- or di-substituted with

R^q , as defined previously; M^b , R^y and R^z are as defined previously;

5 ab) a C_5 - C_7 cycloalkyl group; wherein any one carbon atom in the ring is replaced by a heteroatom selected from the group consisting of O, S, NH and $N(C_{1-4}\text{alkyl})$; and, in which one additional carbon atom may be replaced with NH or $N(C_{1-4}\text{alkyl})$ and in which at least one carbon atom adjacent to each nitrogen heteroatom has both of its attached hydrogen atoms replaced by one oxygen whereby a carbonyl moiety is formed;

10 with the proviso that there are at most two carbonyl moieties present in the ring;

15 ac) a C_2 - C_4 alkenyl radical; wherein the radical is optionally mono-substituted by a substituent selected from the group consisting of any one of a) to ab) or is optionally mono-substituted by substituents selected from the group consisting of phenyl, pyridyl, quinoline and isoquinoline; wherein each phenyl, pyridyl, quinoline or isoquinoline substituent is optionally mono- or di-substituted by R^q , as defined previously;

20 ad) a C_1 - C_4 alkyl radical;

ae) a C_1 - C_4 alkyl mono-substituted by a substituent selected from the group consisting of any one of a) to ad);

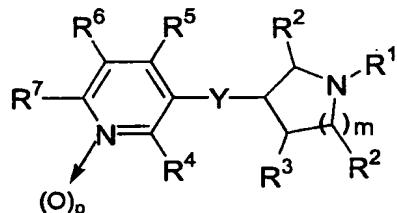
25 af) a 2-oxazolidinonyl moiety; wherein the point of attachment is the nitrogen atom of the oxazolidinone ring; wherein the ring oxygen atom is optionally replaced by a heteroatom selected from the group consisting of S and NR^t (wherein R^t is as defined previously) and one of the saturated carbon atoms of the oxazolidinone ring is optionally mono-substituted by a substituent selected from the group consisting of any one of a) to ae);

30 ag) a C_2 - C_4 alkynyl radical; wherein the radical is independently selected from the group consisting of any one of a) to af) and trialkylsilyl;

ah) phenyl radicals

- ai) bicyclic radicals; wherein the radical is independently selected from the group consisting of naphthyl, biphenyl, quinoline, indolizine, indole, isoindole, indoline, benzofuran, indazole, benzimidazole, purine, quinolizine, cinnoline, quinoxaline, phthalazine and quinazoline;
- 5 aj) heterocyclic radicals; wherein the radical is independently selected from the group consisting of furyl, thienyl, pyrazinyl, pyridazinyl, pyrimidinyl, pyrrolyl, pyrazolyl, imidazolyl, indolyl, thiazolyl, oxazolyl, thiadiazolyl, oxadiazolyl, quinolinyl and isoquinolinyl; and
- 10 ak) aryl and heteroaryl radicals; wherein the radical is independently selected from the group consisting of any one of ah) through aj); wherein the radical is substituted with one or two substituents independently selected from the group consisting of C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆alkoxyC₁-C₆alkyl, C₁-C₆alkoxyC₁-C₆alkoxy, C₁-C₆ thioalkyl, halogen, cyano, hydroxy, amino, nitro and C₁-C₆alkylamino, in which any terminal carbon atom may be replaced by a group selected from the group consisting of carboxyl and C₂-C₆alkoxycarbonyl;
- 15
- 20 and pharmaceutically acceptable salts and esters thereof.

- 16. The method of claim 15 wherein the compound is a selective modulator of the nicotinic acetylcholine receptor.
- 25 17. The method of claim 15 wherein the compound is an antagonist of the nicotinic acetylcholine receptor.
- 18. The method of claim 15 wherein the compound is an agonist of the nicotinic acetylcholine receptor.
- 30 19. The method of claim 15 wherein the condition is acute or chronic pain and the patient is in need of analgesia.



10 wherein

m is selected from 0, 1 or 2;

p is selected from 0 or 1;

15 Y is selected from the group consisting of O, S, S(O) and S(O);

20 R¹ is independently selected from the group consisting of H-, HO-, O-, C₁₋₆alkyl-, C₂₋₆alkenyl-, C₂₋₆alkynyl-, C₃₋₆cycloalkylC₁₋₃alkyl-, phenylC₁₋₃alkyl-, -C(O)C₁₋₆alkyl, -C(O)phenyl, -C(O)C₁₋₆alkylphenyl, -C(O)OC₁₋₆alkyl, -C(O)Ophenyl, -C(O)NHC₁₋₆alkyl, -C(O)N(C₁₋₆alkyl)₂ and -C(O)NHphenyl; wherein R¹ is optionally substituted on a carbon atom with one to three R^a substituents; wherein R^a is independently selected from the group consisting of C₁₋₄alkyl, C₁₋₄alkoxy, hydroxyC₁₋₄alkyl, carbomethoxy, acetoxy, nitro, Cl, Br and F;

25

R² is independently selected from the group consisting of H, C₁₋₆alkyl, phenyl and heteroaryl; wherein heteroaryl is as defined below;

5 R³ is selected from the group consisting of H, C₁₋₆alkyl, Cl, Br and F; with the proviso that if m is 0, then R³ is not Cl, Br or F; and

10 R⁴, R⁵, R⁶ and R⁷ are independently selected from the group consisting of hydrogen and selected radicals; wherein the radicals are selected from the group consisting of:

- 10 a) a trifluoromethyl group: -CF₃;
- b) a halogen atom: -Br, -Cl, -F or -I;
- c) a C₁₋₄alkoxy radical: -OC₁₋₄alkyl; wherein the alkyl is optionally mono- or di-substituted by R^q; wherein

15 R^q is selected from the group consisting of -OH, -OCH₃, -CN, -C(O)NH₂, -OC-(O)NH₂, CHO, -OC(O)N(CH₃)₂, -SO₂NH₂, SO₂N(CH₃)₂, -SOCH₃, SO₂CH₃, -F, -CF₃, -COOM^a (wherein M^a is selected from the group consisting of hydrogen, alkali metal, methyl and phenyl), tetrazolyl (wherein the point of attachment is the carbon atom of the tetrazole ring and one of the nitrogen atoms is mono-substituted by M^a, as defined previously) and -SO₃M^b (wherein M^b is selected from the group consisting of hydrogen and an alkali metal);

20 d) a hydroxy group: -OH;

e) a carbonyloxy radical: -O(C=O)R^s; wherein

25 R^s is a group selected from the group consisting of C₁₋₄alkyl, phenyl and heteroaryl (each of which is optionally mono- or di-substituted with R^q, as defined previously); wherein

30 heteroaryl is a monocyclic aromatic hydrocarbon group having five or six ring atoms, having at least one carbon atom which is the point of attachment; having from one to three carbon atoms replaced by N in the case of six ring atoms, having one carbon atom replaced by O, S or N in the case of five ring

atoms and, optionally, having up to three additional carbon atoms replaced by N;

5 f) a carbamoyloxy radical: $-\text{O}(\text{C}=\text{O})\text{N}(\text{R}^y)\text{R}^z$; wherein R^y and R^z are independently selected from the group consisting of H, $\text{C}_{1-4}\text{alkyl}$ (optionally mono- or di-substituted by R^q , as defined previously), a three to five membered diradical to form a ring wherein R^y and R^z are fused (optionally mono- or di-substituted with R^q , as defined previously) and a two to five membered diradical interrupted by $-\text{O}-$, $-\text{S}-$, $-\text{S}(\text{O})-$ or $-\text{S}(\text{O})_2-$ to form a ring wherein R^y and R^z are fused (optionally mono- or di-substituted with R^q , as defined previously);

10 g) a sulfur radical: $-(\text{S}=(\text{O}))_n\text{R}^s$; wherein n is selected from 0, 1 or 2 and R^s is as defined previously;

15 h) a sulfamoyl group: $-\text{SO}_2\text{N}(\text{R}^y)\text{R}^z$; wherein R^y and R^z are as defined previously;

20 i) an azido radical: N_3 ;

j) a formylamino group: $-(\text{N}-\text{R}^t)-(\text{C}=\text{O})\text{H}$; wherein R^t is selected from the group consisting of H and $\text{C}_{1-4}\text{alkyl}$; wherein the alkyl chain is optionally mono- or di-substituted by R^q , as defined previously;

25 k) a $(\text{C}_{1-4}\text{alkyl})\text{carbonylamino}$ radical: $-(\text{N}-\text{R}^t)-(\text{C}=\text{O})-\text{C}_{1-4}\text{alkyl}$; wherein R^t is as defined previously; wherein the alkyl chain is optionally mono- or di-substituted by R^q , as defined previously;

l) a $(\text{C}_{1-4}\text{alkoxy})\text{carbonylamino}$ radical: $-(\text{N}-\text{R}^t)-(\text{C}=\text{O})-\text{O}-\text{C}_{1-4}\text{alkyl}$; wherein

30 R^t is as defined previously; wherein the alkyl chain is optionally mono-substituted by R^q , as defined previously;

m) a ureido group: $-(\text{N}-\text{R}^t)-(\text{C}=\text{O})\text{N}(\text{R}^y)\text{R}^z$; wherein R^t , R^y and R^z are as defined previously;

n) a sulfonamido group: $-(\text{N}-\text{R}^t)\text{SO}_2\text{R}^s$; wherein R^s and R^t are as defined previously;

o) a cyano group: $-\text{CN}$;

- p) a (C_{1-4} alkyl)carbonyl radical; wherein the carbonyl is acetalized: $-C(OMe)_2C_{1-4}$ alkyl; wherein the alkyl is optionally mono-substituted by R^a , as defined previously;
- q) a carbonyl radical: $-(C=O)R^s$; wherein R^s is as defined previously;
- 5 r) a hydroximinomethyl radical; wherein the oxygen or carbon atom is optionally substituted with a C_{1-4} alkyl group: $-CR^y=NOR^z$; wherein R^y and R^z are as defined previously; with the proviso that R^y and R^z may not be joined together to form a ring;
- 10 s) a (C_{1-4} alkoxy)carbonyl radical: $-(C=O)OC_{1-4}$ alkyl; wherein the alkyl is optionally mono- or di-substituted by R^a , as defined previously;
- t) a carbamoyl radical: $-(C=O)N(R^y)R^z$; wherein R^y and R^z are as defined previously;
- 15 u) a N-hydroxycarbamoyl or $N(C_{1-4}$ alkoxy)carbamoyl radical in which the nitrogen atom may additionally be substituted by a C_{1-4} alkyl group: $-(C=O)-N(OR^y)R^z$; wherein R^y and R^z are as defined previously; with that proviso that R^y and R^z may not be joined together to form a ring;
- v) a thiocarbamoyl group: $-(C=S)N(R^y)R^z$; wherein R^y and R^z are as defined previously;
- 20 w) a carboxyl radical: $-COOM^b$; wherein M^b is as defined previously;
- x) a thiocyanate radical: $-SCN$;
- y) a trifluoromethylthio radical: $-SCF_3$;
- 25 z) a tetrazolyl radical; wherein the point of attachment is the carbon atom of the tetrazole ring and any one nitrogen atom is mono-substituted by a substituent selected from the group consisting of hydrogen, an alkali metal and a C_{1-4} alkyl radical; wherein the C_{1-4} alkyl radical is optionally mono- or di-substituted by R^a , as defined previously;
- 30 aa) an anionic function selected from the group consisting of phosphono [$P=O(OM^b)_2$], alkylphosphono [$P=O(OM^b)-[O(C_{1-4}alkyl)]$], alkylphosphinyl [$P=O(OM^b)-(C_{1-4} alkyl)$], phosphoramido [$P=O(OM^b)N(R^y)R^z$ and $P=O-(OM^b)NHR^x$], sulfino (SO_2M^b), sulfo

(SO₃M^b) and acylsulfonamides selected from the group consisting of CONM^bSO₂R^x, CONM^bSO₂N(R^y)R^z, SO₂NM^bCON(R^y)R^z and SO₂NM^bCN; wherein

R^x is selected from the group consisting of phenyl and heteroaryl; 5 wherein heteroaryl is as defined previously and the phenyl and heteroaryl substituents are optionally mono- or di-substituted with R^q, as defined previously; M^b, R^y and R^z are as defined previously;

ab) a C₅-C₇ cycloalkyl group; wherein any one carbon atom in the ring 10 is replaced by a heteroatom selected from the group consisting of O, S, NH and N(C₁₋₄alkyl); and, in which one additional carbon atom may be replaced with NH or N(C₁₋₄alkyl) and in which at least one carbon atom adjacent to each nitrogen heteroatom has both of its attached hydrogen atoms replaced by one oxygen whereby a 15 carbonyl moiety is formed;

with the proviso that there are at most two carbonyl moieties present in the ring;

ac) a C₂-C₄ alkenyl radical; wherein the radical is optionally 20 mono-substituted by a substituent selected from the group consisting of any one of a) to ab) or is optionally mono-substituted by substituents selected from the group consisting of phenyl, pyridyl, quinoline and isoquinoline; wherein each phenyl, pyridyl, quinoline or isoquinoline substituent is optionally mono- or di-substituted by R^q, as defined previously;

ad) a C₁-C₄ alkyl radical;

ae) a C₁-C₄ alkyl mono-substituted by a substituent selected from the 25 group consisting of any one of a) to ad);

af) a 2-oxazolidinonyl moiety; wherein the point of attachment is the nitrogen atom of the oxazolidinone ring; wherein the ring oxygen 30 atom is optionally replaced by a heteroatom selected from the group consisting of S and NR^t (wherein R^t is as defined previously) and one of the saturated carbon atoms of the oxazolidinone ring is optionally

mono-substituted by a substituent selected from the group consisting of any one of a) to ae);

5 ag) a C₂-C₄ alkynyl radical; wherein the radical is independently selected from the group consisting of any one of a) to af) and trialkylsilyl;

ah) phenyl radicals

10 ai) bicyclic radicals; wherein the radical is independently selected from the group consisting of naphthyl, biphenyl, quinoline, indolizine, indole, isoindole, indoline, benzofuran, indazole, benzimidazole, purine, quinolizine, cinnoline, quinoxaline, phthalazine and quinazoline;

15 aj) heterocyclic radicals; wherein the radical is independently selected from the group consisting of furyl, thienyl, pyrazinyl, pyridazinyl, pyrimidinyl, pyrrolyl, pyrazolyl, imidazolyl, indolyl, thiazolyl, oxazolyl, thiadiazolyl, oxadiazolyl, quinolinyl and isoquinolinyl; and

20 ak) aryl and heteroaryl radicals; wherein the radical is independently selected from the group consisting of any one of ah) through aj); wherein the radical is substituted with one to two substituents independently selected from the group consisting of C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ alkoxyC₁-C₆ alkyl, C₁-C₆ alkoxyC₁-C₆ alkoxy, C₁-C₆ thioalkyl, halogen, cyano, hydroxy, amino, nitro and C₁-C₆ alkylamino, in which any terminal carbon atom may be replaced by a group selected from the group consisting of carboxyl and C₂-C₆ alkoxycarbonyl;

and pharmaceutically acceptable salts and esters thereof.

22. The pharmaceutical composition of claim 21 wherein the condition is acute or chronic pain and the patient is in need of analgesia.

23. The pharmaceutical composition of claim 21 wherein the condition or disease is Alzheimer's disease, memory loss or dementia or loss of motor function.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 99/18954

A. CLASSIFICATION OF SUBJECT MATTER IPC 7 C07D401/12 C07D401/14 A61K31/4427																
According to International Patent Classification (IPC) or to both national classification and IPC																
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) IPC 7 C07D A61K																
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched																
Electronic data base consulted during the international search (name of data base and, where practical, search terms used)																
C. DOCUMENTS CONSIDERED TO BE RELEVANT <table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th style="text-align: left; padding: 2px;">Category</th> <th style="text-align: left; padding: 2px;">Citation of document, with indication, where appropriate, of the relevant passages</th> <th style="text-align: left; padding: 2px;">Relevant to claim No.</th> </tr> </thead> <tbody> <tr> <td style="text-align: center; padding: 2px;">X, P</td> <td style="padding: 2px;">WO 99 24422 A (NIELSEN ELSEBET OESTERGAARD ;NEUROSEARCH AS (DK); OLSEN GUNNAR M () 20 May 1999 (1999-05-20) the whole document ---</td> <td style="text-align: center; padding: 2px;">1-23</td> </tr> <tr> <td style="text-align: center; padding: 2px;">X</td> <td style="padding: 2px;">EP 0 107 930 A (ROBINS CO INC A H) 9 May 1984 (1984-05-09) preparations 12,19 ---</td> <td style="text-align: center; padding: 2px;">1</td> </tr> <tr> <td style="text-align: center; padding: 2px;">X</td> <td style="padding: 2px;">US 4 667 031 A (LILJE KENNETH C) 19 May 1987 (1987-05-19) column 3; claims 5,12 ---</td> <td style="text-align: center; padding: 2px;">1</td> </tr> <tr> <td></td> <td style="text-align: center; padding: 2px;">-/-</td> <td></td> </tr> </tbody> </table>		Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.	X, P	WO 99 24422 A (NIELSEN ELSEBET OESTERGAARD ;NEUROSEARCH AS (DK); OLSEN GUNNAR M () 20 May 1999 (1999-05-20) the whole document ---	1-23	X	EP 0 107 930 A (ROBINS CO INC A H) 9 May 1984 (1984-05-09) preparations 12,19 ---	1	X	US 4 667 031 A (LILJE KENNETH C) 19 May 1987 (1987-05-19) column 3; claims 5,12 ---	1		-/-	
Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.														
X, P	WO 99 24422 A (NIELSEN ELSEBET OESTERGAARD ;NEUROSEARCH AS (DK); OLSEN GUNNAR M () 20 May 1999 (1999-05-20) the whole document ---	1-23														
X	EP 0 107 930 A (ROBINS CO INC A H) 9 May 1984 (1984-05-09) preparations 12,19 ---	1														
X	US 4 667 031 A (LILJE KENNETH C) 19 May 1987 (1987-05-19) column 3; claims 5,12 ---	1														
	-/-															
<input checked="" type="checkbox"/> Further documents are listed in the continuation of box C. <input checked="" type="checkbox"/> Patent family members are listed in annex.																
* Special categories of cited documents : "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier document but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed																
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "S" document member of the same patent family																
Date of the actual completion of the international search 25 November 1999																
Date of mailing of the international search report 09/12/1999																
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016																
Authorized officer Bosma, P																

INTERNATIONAL SEARCH REPORT

International Application No
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A, P	<p>CHEMICAL ABSTRACTS, vol. 129, no. 13, 28 September 1998 (1998-09-28) Columbus, Ohio, US; abstract no. 156451r, BASMAJIAN, G. P. ET AL: "Design of novel nicotinic acetylcholine receptor agonists with potential antinociceptive activity" page 20; XP002123864 abstract & PAIN MECH. MANAGE., 'INT. SYMP. APPL. THEORY METAB. REGUL. PAIN! (1998), MEETING DATE 1996, 285-300. EDITOR(S): AYRAPETYAN, SINERIK N.;APKARIAN, A. VANIA. PUBLISHER: IOS PRESS, AMSTERDAM, NETH. , ----</p>	1,15-23
A	<p>US 5 629 325 A (LIN NAN-HORNG ET AL) 13 May 1997 (1997-05-13) cited in the application claims 1-9; examples -----</p>	1,15-23

INTERNATIONAL SEARCH REPORT

Int. national application No.

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Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: 15-20
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 15-20
are directed to a method of treatment of the human/animal
body, the search has been carried out and based on the alleged
effects of the compound/composition.
2. Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such
an extent that no meaningful International Search can be carried out, specifically:
3. Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this International Search Report covers all
searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment
of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report
covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is
restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT
Information on patent family members

 International Application No
 PCT/US 99/18954

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
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